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COVID–19 AND BEYOND: OVERSIGHT OF THE FDA'S FOREIGN DRUG MANUFACTURING INSPECTION PROCESS

HEARING

BEFORE THE

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COVID–19 AND BEYOND: OVERSIGHT OF THE FDA'S FOREIGN DRUG MANUFACTURING INSPECTION PROCESS

TUESDAY, JUNE 2, 2020

U.S. SENATE,
COMMITTEE ON FINANCE,
Washington, DC.

The WebEx hearing was convened, pursuant to notice, at 2:30 p.m., in Room SD–106, Dirksen Senate Office Building, Hon. Chuck Grassley (chairman of the committee) presiding.

Present: Senators Cornyn, Thune, Toomey, Cassidy, Daines, Wyden, Stabenow, Menendez, Carper, Cardin, Brown, Whitehouse, Bennet, Casey, Warner, Hassan, and Cortez Masto.

Also present: Republican staff: Joshua Flynn-Brown, Deputy Chief Investigative Counsel; and Charles Pankenier, Detailee. Democratic staff: David Berick, Chief Investigator; Peter Gartrell, Investigator; and Joshua Sheinkman, Staff Director.

OPENING STATEMENT OF HON. CHUCK GRASSLEY, A U.S. SENATOR FROM IOWA, CHAIRMAN, COMMITTEE ON FINANCE

The CHAIRMAN. Good afternoon, everybody. I want to welcome everyone to the Finance Committee oversight hearing on Food and Drug Administration's foreign drug manufacturing inspection process. This committee has an obligation to ensure drugs paid for by the taxpayers, whether it is Medicare or Medicaid, satisfy quality standards and are safe and effective for patients.

Second, besides taxpayer concerns, this committee has jurisdiction over trade, and we have responsibilities to guarantee only quality pharmaceuticals enter the United States. That responsibility, both of Congress and the FDA, is heightened now that we are living through the COVID pandemic. Whether we are in the midst of a pandemic or not, these supply chain issues must be shored up and solved.

Starting in June of last year, I began oversight activities on this issue. I wrote letters at that time to Secretary Azar and Acting FDA Commissioner Dr. Sharpless. I asked a series of questions relating to manufacturing facilities overseas that manufacture final dosages for drugs and active pharmaceutical ingredients. And I am going to refer to "active pharmaceutical ingredients" throughout the day as APIs. I also asked how the Food and Drug Administration manages its foreign inspection regime.

The Government Accountability Office has said that the FDA does conduct some unannounced inspections overseas, but they do

not have data on the frequency. However, the Government Accountability Office noted in 2019 that the FDA estimated that they generally provided 12 weeks of notice before the inspection.

So, simply said, FDA then is undermining the ability of field inspectors to do their job. Twelve weeks, common sense tells me, is plenty of time to doctor up a facility to make sure that it passes inspection. Yet incredibly, some facilities still get caught. That is how bad it is, and we have to do something about it. The result is that the consumer is put at risk.

According to the most recent FDA data, the United States has 46 percent of finished dosage form facilities. That is where API are turned into final form such as tablets. That means over 50 percent of the sites manufacturing finished drugs are located outside the United States. But that is just part of the story.

What we really need to know is, where did the API come from? According to the most recent FDA data, 13 percent comes from China, 19 percent from India. Combined, that is more than any other country. And overall then, more than 70 percent of facilities that make APIs are located overseas.

These figures, coupled with the COVID pandemic, have garnered a lot of attention, including what might need to be done from a national security standpoint. But the figures do not make clear what needs to be done from a drug safety perspective.

We need to have a robust and aggressive foreign inspection program. Now, with respect to China and India, both those countries have had serious quality control problems. We all remember the valsartan recall, where that drug was found to contain contaminants used in rocket fuel. Facilities in China and India produce that drug. We also should not forget Heparin, and that is a scandal all by itself. In that case, patients undergoing dialysis began to have severe and life-threatening side effects because the manufacturing plant in China introduced a toxin into the production chain.

Hundreds of people died, and hundreds were sickened. And then we have Ranbaxy, an Indian manufacturer. Ranbaxy's production chain exposed drugs to potential cross-contamination by penicillin and used APIs from facilities that were not approved by the FDA. That company also manufactured Lipitor and was shut down because it could not explain why some of those tablets had pieces of glass in them.

I fear these examples are just the tip of iceberg. They show why the FDA must maintain an aggressive inspection machine to ensure drug quality, but at the same time also impose a strong enforcement regime on bad actors.

In February of this year, FDA Commissioner Hahn told me that in Fiscal Year 2018 the Center for Drug Evaluation and Research issued almost five times as many warning letters for human drug manufacturers as compared to 2015. He said that is a sign that FDA is better able to use its resources for identifying problems.

Now that is very good: stay aggressive and do not hesitate to be more aggressive. On the front end, though, that process should include unannounced inspections overseas. After all, why would we give manufacturers time to prepare their facilities for inspection? They ought to be looking over their shoulder every day. That would keep them honest.

During the Obama administration, we had what was called the India Pilot Program. It allowed for no-warning inspections, or a couple of days' worth of warning. Under it, the FDA issued a 60-percent increase in what are termed "official action indicated" findings. In 2015, the Obama administration shut the pilot program down, and I believe that there was no explanation of why.

It sounds like the program was a victim of its own success. Now, this issue is a very bipartisan issue. Republican and Democrat administrations have come up short. The Government Accountability Office has a body of work from multiple administrations that proves that this is bipartisan. For example, both the Obama and Trump administrations have struggled to fill vacancies in foreign offices. So that brings us to today, as what I have just said is what we found out from over a year or more of investigations without a hearing.

Today we have witnesses from the FDA. They can speak to all these issues and how the pandemic has impacted their work. On the first panel we have FDA witnesses and a Government Accountability witness. On the second panel, we have private-sector companies.

So I thank all of you for being here. It is important to note that I plan to follow up with another hearing soon examining another problematic aspect for the medical supply chain, specifically, the increase in trade of fake and faulty personal protective equipment. That is separate from what we will discuss today.

In closing, I want to say two things. First, thank you to FDA officials who work tirelessly to inspect facilities overseas. Second, regardless of party, we must have an honest discussion of the government's shortcomings so that we can better understand what we as Congress can do to ensure drug safety for the taxpayers. After all, we work for them and must always answer to them.

One thing before I introduce Ranking Member Wyden, and that is simply to say that we have one more vote in a series that started at 2:15. We will continue to go through that vote, and we also have a vote at 4:30, and we will continue to go through that vote.

[The prepared statement of Chairman Grassley appears in the appendix.]

So, Senator Wyden, are you ready?

Senator WYDEN. I am, Mr. Chairman. Would you like me to proceed now?

The CHAIRMAN. Please do.

OPENING STATEMENT OF HON. RON WYDEN, A U.S. SENATOR FROM OREGON

Senator WYDEN. This afternoon, the Finance Committee is holding its first meeting since March, focusing on the FDA's failure to adequately inspect foreign drug manufacturers for safety. In my view, the head of the FDA ought to be at this hearing to face tough questions on this issue, but FDA Commissioner Hahn is not with us today for one reason, and that is because the Trump administration blocked his testimony. The Trump administration did this to prevent the committee from holding the point person for the FDA accountable.

I also asked for the committee to invite the journalist Katherine Eban to testify, because she has literally written the book on this issue. That also, unfortunately, has not happened.

In lieu of that, I would ask unanimous consent to enter into the record testimony and articles from Ms. Eban on this subject.

The CHAIRMAN. Without objection, so ordered.

[The documents appear in the appendix beginning on p. 174.]

Senator WYDEN. Thank you, Mr. Chairman.

While the committee meets for this hearing, COVID–19 is ripping through nursing homes and killing thousands of Americans each week. Unemployment is at near-Depression levels. The kindling laid down over the centuries of racial injustice was reignited by the murder of George Floyd. The President is agitating for more violence and more escalation as our Nation suffers.

The injustice driving peaceful protesters to the streets over the last few days is woven throughout society. Since the committee is dealing with health care in this hearing, I am going to start my remarks with an immediate piece of urgently needed health-care reform. COVID–19 has hit the African American community harder than virtually any other group of Americans. I would note, the recent analysis that was described in *The Washington Post* showed that counties that are majority black had three times the rate of infections and almost six times the rate of deaths as counties where white residents are in the majority.

The racial injustice status quo is simply immoral, with the long terrible history of our health-care system working against black people in America, from simply not listening when symptoms are reported, up to performing cruel experiments on black human beings. That is part of why COVID–19 is having such an out-sized impact on the African American community. There is a risk, for example, that when a COVID–19 vaccine becomes available, vaccination rates in the African American community may be lower because many in the community, for understandable reasons, do not believe that American health care is really looking out for them and is really going to give them a fair shake.

So I want to make something very clear right now. This committee has real muscle when it comes to Federal health-care spending and doing something about what I just described. Two trillion dollars in spending over flagship programs like Medicare and Medicaid, the Affordable Care Act, and more are inside the jurisdiction of the Finance Committee.

So today, in the beginning, I am calling on this committee to come together and use all of that power and authority to right the wrongs of the past that I have described this afternoon. On our watch, colleagues, this just has to get done.

Now, as to the subject of today's hearing, I want to focus on one specific example of the FDA and the President teaming up to put Americans in danger. I want to talk about hydroxychloroquine. Back in March, with the pandemic exploding nationwide, far-right media began talking about using this old malaria drug to treat COVID–19. The President seized on the report, without any valid evidence, and spent weeks declaring it to be the ultimate game changer in the fight against this horrible pandemic. The FDA, in my view, bowed to pressure and issued what's called an emergency

use authorization for the drug. Doing so throws open the doors to tens of millions of pills, including some directly related to this hearing, manufactured inside facilities in Pakistan and India that have either failed FDA inspection or never been inspected by the FDA at all.

Studies have now shown that the drug has no benefit for COVID patients. In fact, it is actually linked to higher rates of COVID–19 mortality. On April 24th, the Food and Drug Administration warned against using the drug in COVID treatment, and they said there were serious, I quote here, "serious and potentially life-threatening heart rhythm problems," unquote. The FDA says it still can be imported from unapproved manufacturing facilities.

A recent article in *The New England Journal of Medicine* said the episode posed, and I quote, "fundamental threats to the U.S. drug evaluation process." Mr. Chairman, without objection, I would like to have that article from *The New England Journal of Medicine* put into the record at this point.

The CHAIRMAN. Without objection, so ordered.

[The article appears in the appendix on p. 194.]

Senator WYDEN. The fact is, lots of Americans take this medication to treat other diseases, including lupus and rheumatoid arthritis. It is prescribed by their doctors as part of a valid treatment. They are counting on having a safe supply of their medication, and it seems Donald Trump has pretty much taken that away from them. He repeated a bunch of far-right pundits touting junk science. Now the U.S. market is polluted with tens of millions of hydroxychloroquine doses that may or may not be safe. It is not clear that there is a system in place to distinguish them from other stockpiles that came from unapproved sources.

So if you are talking about FDA failures leading to greater risk for Americans, hydroxychloroquine is the case in point. There is also the botched roll-out of COVID–19 antibody tests. There is the emergency use authorization for faulty K–95 masks that pose a danger to health-care workers and first responders. There is the fact that the number of FDA inspections for foreign drug manufacturing facilities was already down under the Trump administration.

Now on this committee, we know that there is bipartisan interest in seeing improvements at the FDA. It makes sense for us to build our drug manufacturing capacity in America. However, the Trump administration just handed a big contract for COVID–19 drug manufacturing to a company with no experience in manufacturing drugs and no facilities in which to manufacture them. That is not good enough in my view, Mr. Chairman and colleagues. It is not a good enough plan to help COVID patients who are suffering right now.

It also raises questions about how this administration would handle a COVID–19 vaccine if and when a vaccine becomes available. There is much to account for on this issue. The Trump administration's continuing efforts to stonewall our oversight by blocking Commissioner Hahn from answering our questions today is preventing real, actual accountability.

Still, I want to make it clear to our witnesses who are here with us, we thank them for doing so, and I look forward to their testimony.

Thank you, Mr. Chairman.

[The prepared statement of Senator Wyden appears in the appendix.]

The CHAIRMAN. One clarification. The Trump administration did allow Commissioner Hahn to show, but we decided for the purpose of the issues of this hearing, which deal with the importation of some less-than-quality products from foreign countries, that having additional FDA witnesses would fill a very important gap in knowledge for our committee.

I am going to introduce Mark Abdoo, Associate Commissioner for Global Policy and Strategy, providing executive oversight, strategic leadership, and policy direction to FDA's global operations, trade and diplomacy activity, and engagement with international stakeholders. He leads the Office of Global Policy and Strategy, which is comprised of the Office of Diplomacy and Partnership, the Office of Global Operations, and the Office of Trade, Mutual Recognition, and International Arrangements—which are collectively dedicated to expanding the reach of FDA's global agenda in sustainable and measurable ways.

Judith McMeekin is Associate Commissioner for Regulatory Affairs and has responsibility for 5,000 staff and operations within the Office of Regulatory Affairs. The Office of Regulatory Affairs is FDA's field force supporting FDA's product center through responsibilities including inspections and investigations, criminal investigations, compliance with enforcement, import operations, regulatory science, and field laboratory operations.

Dr. Douglas Throckmorton is Deputy Director of Regulatory Programs at the Office of Drug Evaluation and Research. Dr. Throckmorton is a board-certified physician. He carries the responsibility for overseeing the regulation of research development; manufacturing; marketing of prescription, over-the-counter, and generic drugs in the United States; and ensuring that the benefits of approved drugs outweigh their known risks.

Dr. Mary Denigan-Macauley oversees the U.S. Government Accountability Office's portfolio of audits on public health, private health, and the markets associated with them, including opioid issues. Mary joined GAO in 2001, managing a diverse portfolio related to science, agricultural production, and defense on GAO's Natural Resource and Environment team. This work covered crosscutting topics such as antibiotic resistance, food safety, and emergency preparation.

As the witnesses know, we are under time restrictions at the moment. And accordingly, the three FDA witnesses will try to keep their opening statements to a combined 7½ minutes. And then GAO will have the equal 7½ minutes.

We will begin with Mr. Abdoo.

Senator WYDEN. Mr. Chairman?

The CHAIRMAN. Yes; go ahead.

Senator WYDEN. If I could, just for a minute, with respect. We still feel, for real accountability over all the issues we are discussing today, you have got to have Dr. Hahn. And in fact, all of

the employees that you just described, we certainly recognize their role at the FDA. They all report to Dr. Hahn.

So, respectfully, we have a difference of opinion. I think it is very unfortunate that he is not with us today, because he is the person who is really accountable for the entire array of issues we are discussing today, and I appreciate the chance to respond briefly.

The CHAIRMAN. The only thing I would give back to you is that these witnesses are the experts and cover the bases that we are interested in for this hearing.

Mr. Abdoo, would you proceed, please?

STATEMENT OF MARK ABDOO, ASSOCIATE COMMISSIONER FOR GLOBAL POLICY AND STRATEGY, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, SILVER SPRING, MD

Mr. ABDOO. Chairman Grassley, Ranking Member Wyden, members of the committee, I am Mark Abdoo, Associate Commissioner for Global Policy and Strategy. As Chairman Grassley noted, I lead the FDA's Office of Global Policy and Strategy by oversight, leadership, and policy direction to our global operations in trade, and diplomacy activities and engagement with international stakeholders.

Thank you for the opportunity to discuss FDA's international pharmaceutical oversight today. Over the past 30 years, pharmaceutical manufacturing has become increasingly a global enterprise. Beginning in the 1970s, industry moved away from the mainland United States, first to Puerto Rico in response to tax incentives and then to Europe and nations that were developing at the time such as China and India, which offer significantly lower labor, energy, and transportation costs.

Globalization presented substantial challenges to regulatory oversight. FDA has responded with a comprehensive strategy to facilitate greater coordination and oversight of medical products. In addition to increasing foreign inspections, our efforts have included the following: developing new enforcement and regulatory tools; increasing collaboration with foreign regulators and other stakeholders; developing internationally harmonized standards and standard convergence; educating foreign industry about FDA requirements; and increasing transparency and accountability in the supply chain.

Responsibility for addressing these global challenges is distributed across the agency. My office serves as a focal point for FDA-wide coordination and information-sharing and a point of access to multilateral organizations, addresses issues related to international trade of regulated products, negotiates mutual recognition agreements, enters into arrangements that facilitate foreign inspections and the sharing of information with global regulatory counterparts, and manages FDA's foreign offices around the world.

We have made progress in recent years in developing the foreign base inspectorate; staffing at the foreign offices is at historically high levels. Our foreign offices conduct inspections, particularly unannounced for-cause inspections. They also work with regulatory counterparts in-country, engage in outreach education and training with industry associations, promote good manufacturing practices including data integrity and quality, and provide boots-on-the-

ground data and analysis to inform decision-making at FDA headquarters.

In recent years, we also completed the historic Mutual Recognition Agreement between FDA and the European Union, which is now beginning to yield benefits. The MRA enables FDA and EU regulatory authorities to rely on information from routine drug inspections conducted within each other's borders.

As implementation continues and more information is exchanged, the MRA will help to further minimize duplication of drug inspections, lower inspection costs, and permit us to devote more resources to other parts of the world where there may be greater risks.

We are deeply committed to leveraging all of our resources to protect the reliability and availability of the drugs to treat Americans.

Thank you again for the opportunity to be here today.

[The prepared statement of Mr. Abdoo appears in the appendix.]

The CHAIRMAN. Dr. McMeekin?

STATEMENT OF JUDITH McMEEKIN, Pharm.D., ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, SILVER SPRING, MD

Dr. MCMEEKIN. Chairman Grassley, Ranking Member Wyden, and members of the committee, I am Judith McMeekin, Associate Commissioner for Regulatory Affairs at the Food and Drug Administration. Thank you for the opportunity to discuss FDA's foreign drug inspection program.

Protecting public health is the FDA mission, and it is the foundation of all of our work. Americans can be confident in the quality of FDA-regulated products. Whether a drug or food is produced in the United States or overseas, products must undergo the same rigorous process, and the information must be fully reviewed by our highly trained scientific staff.

The FDA inspects manufacturing facilities around the world. As the products we regulate globalize, it is important for us to modernize our policies and processes to ensure that companies, regardless of where they are located, meet the FDA's strict standards.

The FDA's drug inspection program shifted from one focused heavily on the U.S.-based facilities through the early 2000s to programs that, since 2015, have conducted more foreign than domestic drug inspections. Consistent with domestic oversight, the FDA's strategy for overseeing the safety of imported products is to maximize the agency's public health impact by aligning resource allocations to risk levels and tailoring the use of regulatory tools accordingly.

In the foreign arena, the FDA does not draw upon the same enforcement mechanisms or have a comparable level of infrastructure. For example, if a domestic firm refuses inspection, we are able to seek an inspection warrant. But we do not have the same capacity in foreign countries. To supplement our foreign oversight, the agency utilizes additional tools to ensure the safety and efficacy of products, including but not limited to import targeting systems; border surveillance including import alerts, import certification,

and enhanced import screening to identify products for sampling; and conducting foreign inspections.

The FDA optimizes our oversight of foreign manufacturers by leveraging the work of partners with strong regulatory systems and responsible parties in the supply chain. During the COVID–19 pandemic, the FDA continues to utilize and implement alternative inspection tools and approaches while postponing foreign and domestic routine surveillance facility inspections.

This approach will continue, as conditions warrant, with the exception of certain mission-critical inspections, including preapproval and for-cause assignments. Importantly, during this interim period, we are evaluating additional ways to conduct our inspection work that would not jeopardize public safety and protects both the firms and the FDA staff.

FDA is utilizing all available tools to oversee the safety and quality of FDA-regulated products for all Americans. Foreign inspections present the agency with unique challenges, including the hiring and retention of qualified investigators. I am committed to taking an assessment of our inspection process and identifying opportunities for improvement, ways to optimize and streamline processes using technology and innovation, to be more efficient, and modernize our approach.

I welcome continued discussion with the committee and others. Thank you again for the opportunity to be here today, and I look forward to answering your questions.

[The prepared statement of Dr. McMeekin appears in the appendix.]

The CHAIRMAN. Thank you very much. Now we call on Dr. Mary Denigan-Macauley.

STATEMENT OF MARY DENIGAN-MACAULEY, Ph.D., DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE, WASHINGTON, DC

Dr. DENIGAN-MACAULEY. Thank you, Chairman Grassley, Ranking Member Wyden, and members of the committee, for the opportunity to discuss our work on FDA's foreign drug inspection program.

The COVID–19 pandemic has called greater attention to the United States' reliance on foreign drug manufacturers and highlights the importance of a secure pharmaceutical supply chain.

Like most drugs manufactured for the U.S. market, many that are important for treating COVID–19 are manufactured overseas. This includes antibiotics for secondary respiratory infections and sedatives for ventilating patients. Today, the majority of establishments manufacturing drugs are overseas. Americans must have access to safe but effective drugs. However, we have had longstanding concerns about FDA's ability to oversee the increasingly global supply chain.

In 1998, we reported that FDA had significant problems managing its foreign inspection data and conducted infrequent inspections of foreign establishments compared to what they did domestically. Since then, we have returned to the topic multiple times and found that problems persist. In 2008 for example, we determined that FDA data were not sufficient to know how many foreign drug

establishments were subject to inspection. In addition, FDA continued to inspect relatively few foreign establishments, and when it did, investigators faced challenges that influenced how the inspections were conducted.

For example, unlike in the U.S., where an establishment has no notice that an investigator is coming, FDA routinely gave foreign manufacturers significant notice. And FDA investigators relied on English-speaking employees of the establishment that they were inspecting to translate key documents, including those demonstrating compliance with good manufacturing practices.

In 2010, we found that while FDA was conducting more inspections overseas, many establishments still had never been inspected. We also identified shortcomings in the operations of foreign offices FDA opened to provide the agency with in-country information and inspection capability. In 2010 and 2016, we found that these offices faced persistently high vacancy rates, raising questions about their effectiveness. As a result of these and other challenges, we added FDA's oversight of medical products to GAO's high-risk list.

Last December, we reported that from 2012 to 2016 FDA increased the number of foreign inspections it conducted. And in 2015, FDA had, for the first time, conducted more foreign inspections than domestic. A growing percentage of these were in China and India, which have the largest number of establishments manufacturing drugs for the United States. However, as Senator Grassley noted, we also found that FDA still provided up to a 3-month advance notice for most foreign inspections, which could give establishments a chance to fix the problems before an investigator even arrives.

Investigators also continued to face persistent challenges when they traveled overseas. As we learned on our site visits to India and China, and in conversation with investigators, a single investigator often had to inspect manufacturing campuses covering hundreds of acres of land in rural areas. Most have little flexibility to extend their time at a facility. Travel schedules required back-to-back inspections.

FDA also continued to send inspectors into establishments without translators. We were told this was particularly difficult in Japan and China. Investigators also had to rely on translators provided by the same drug manufacturer that they were inspecting, raising questions about the accuracy of the information. One investigator told us they had to resort to a translation app on their phone. We also found that from 2016 to 2018 both foreign and domestic inspections had decreased. FDA attributed the decline in part to continued vacancies among investigators available to conduct these investigations.

While FDA has made progress over the years, these persistent challenges raise questions about its ability to conduct inspections overseas that are equivalent to those done here in the United States. The pandemic has further complicated the playing field. In March, as has already been noted, the agency announced it had postponed nearly all inspections of foreign manufacturing establishments. While FDA notes that it has other tools to ensure the safety of the U.S. drug supply, the lack of foreign inspections re-

moves a critical source of information about the quality of the drugs that are manufactured for our U.S. market.

Further, it is unclear the effect COVID will have on FDA's ability to fill those persistent vacancies, both in foreign offices and among the U.S.-based inspectors who conduct most of the inspections overseas. And it is unclear what the effect will be on FDA's ability to gather that critical in-country information to help determine, for example, which establishments are at highest risk.

Thank you, Chairman Grassley, Ranking Member Wyden, and members of the committee, for holding this hearing. This concludes my prepared remarks. I am happy to respond to any questions you may have.

[The prepared statement of Dr. Denigan-Macauley appears in the appendix.]

Senator CORNYN [presiding]. Thank you for your testimony. I see one of your credentials, Mary, is having taught at Sam Houston State University, so it's good to have you as a witness here today.

Dr. DENIGAN-MACAULEY. Thank you.

Senator CORNYN. Dr. Throckmorton will be the next witness. He is the Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research, Food and Drug Administration. Dr. Throckmorton?

STATEMENT OF DOUGLAS C. THROCKMORTON, M.D., DEPUTY DIRECTOR FOR REGULATORY PROGRAMS, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, SILVER SPRING, MD

Dr. THROCKMORTON. Chairman Grassley, Ranking Member Wyden, and members of the committee, I am Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs at the Center for Drug Evaluation and Research in the FDA. Thank you for inviting me to participate in this important discussion. Protecting the safety, quality, and availability for Americans is at the heart of everything we do at the FDA. To accomplish this, we use several tools.

Today's hearing is focused on inspections, which are one important part of a robust, multipronged approach to overseeing the safety and quality of FDA-regulated products. While important, inspections are not the only impetus for drug quality. First and foremost, the firms manufacturing these products have the primary responsibility to reliably produce quality products. Sponsors are required to comply with good manufacturing practices to assure the identity, strength, and purity of their products and to provide routine quality testing.

CDER and FDA support this work by providing guidance to them about best manufacturing practices, critically assessing adverse events to spot manufacturing issues, actively surveilling drug quality, and applying post-marketing study requirements to identify and evaluate emerging drug safety signals.

The goal of all of these efforts is to protect the public health. We also partner with the FDA's ORA to maximize the values of those inspections. Additionally, other safety initiatives include proactive testing by FDA of selected pharmaceutical ingredients and finished dosage-form drugs in our state-of-the-art laboratories.

Only a small percentage, about 1 percent of drugs, that are tested fail to meet the established quality specifications. Additionally, the manufactured quality problems we do identify are similar for both U.S. and foreign facilities. We also collect data about safety and quality of the drugs once they are on the market. And just this week, CDER released our fifth annual report entitled "Drug Safety Priorities: 2019" detailing our key safety programs and activities, and highlighting the depth and versatility of our drug safety initiatives across CDER.

All these checks and rechecks are needed because much of pharmaceutical manufacturing still operates with decades-old approaches and technologies. CDER's vision is to spur the industry to modernize so the quality can be consistently and reliably built into each tablet or vial they produce. This includes initiatives to encourage advanced manufacturing technologies and quality management maturity. While time does not permit me to go into detail, I would welcome the opportunity to discuss these proactive strategies. CDER believes they would yield important benefits for both quality and safety.

Importantly, these advanced manufacturing techniques provide a safer and more secure drug supply chain and may promote a shift to more U.S. domestic pharmaceutical manufacturing. I look forward to working with the committee to protect the reliability and availability of drugs to treat Americans, and to strengthen investments in modern manufacturing technology.

Thank you, very much.

[The prepared statement of Dr. Throckmorton appears in the appendix.]

Senator CORNYN. Thank you, Dr. Throckmorton. We will now go to rounds of questioning. The chairman has gone to vote, so he has asked me to chair in his absence.

I would like to change the topic just slightly, but it seems to me if there is one thing that COVID–19 has taught us, it is that we cannot rely on supply chains coming from outside of our country. We have long become accustomed to being able to buy cheaper products because they are manufactured in other countries with the lower overhead, labor, and other costs, but obviously this pandemic has demonstrated, at least to me, the importance of onshoring a lot of our most basic functions—things like medical equipment, things like drugs.

And I would just like to get the reaction of the witnesses. Am I wrong? Do you think we are stuck with this dispersed global supply chain that can be disrupted in the next pandemic? Or do you think there are steps, as a matter of sound public policy, that the Congress ought to consider in terms of bringing that capacity for manufacturing back onshore?

So, Dr. McMeekin, would you care to take a stab at that?

Dr. MCMEEKIN. Sure; thank you. American consumers should know that the U.S. drug supply is safe and supply chains are secure. The U.S. drug supply is among the safest in the world. FDA thoroughly reviews drug applications to ensure that medications are safe and effective before they reach the market and oversees drug quality post-approval.

Senator CORNYN. Excuse me just a second. Did you say our supply chains are secure?

Dr. MCMEEKIN. Yes.

Senator CORNYN. How much of our active pharmaceutical ingredients for our drugs in America depend on China?

Dr. MCMEEKIN. I am going to refer to Doug. Doug, can you add to the——

Senator CORNYN. And how much do we depend on India? Pardon me. Dr. Throckmorton, go ahead.

Dr. THROCKMORTON. For active pharmaceutical ingredients, the U.S. provides about 28 percent; China, about 13 percent; and India, 18 percent.

Senator CORNYN. So I mean they are as secure as the supply from China and from India is, at least for the percentage that they contribute, but I seem to remember that there was at least one instance during the pandemic where hydroxychloroquine was being hoarded by one of the countries that ordinarily is a source for that drug. Do I remember that incorrectly? Or do you recall that?

Dr. MCMEEKIN. We do have imports of products, and the FDA uses additional tools to help complement our inspections, including remote assessments of foreign manufacturing firms.

Senator CORNYN. I am sorry. I am not talking about inspections now. I am sorry if I was not clear. I am just talking about, in the midst of the next pandemic, what percentage of the pharmaceuticals, the active pharmaceutical ingredients that we depend upon in the United States, are vulnerable, or are in jeopardy because that supply comes from a country—let us say in this instance, where China obviously has been the main source of personal protective equipment, but after the virus broke out they obviously delayed notifying the World Health Organization and other countries around the world why they had hoarded personal protective equipment.

It seems to me the same thing could happen to our drug supply. Am I wrong?

Dr. MCMEEKIN. The foreign establishments and the domestic establishments are held to the same standards. The standards are the same, whether you are foreign or you are domestic. We follow the same process to inspect them. We have the same standards to inspect them, and they are held to the same high standards of FDA requirements.

Senator CORNYN. So the percentage of the active pharmaceutical ingredients that we get from China—if for some reason China is either unwilling or unable to continue supplying that, does that not strike you as a vulnerability for the United States and our public health?

Dr. MCMEEKIN. It would be good to have redundant systems.

Senator CORNYN. Do any of you care to venture what it is that the U.S. Congress might do as a matter of sound public policy to encourage more manufacturing of active pharmaceutical ingredients here in the United States, as opposed to depending on these supply chains overseas?

Dr. THROCKMORTON. Senator, I might take a stab at that one. I will just echo what you said. We do need a robust, reliable supply

source for all of our drugs for the American public. No question at all.

We do believe that there are things that we can do as a country that would encourage additional on-shoring. As I mentioned in my testimony, we believe that the advanced manufacturing practices that U.S. firms currently employ put us ahead of what is seen in the rest of the world. And to the extent we could encourage and support the adoption of those, it would reduce costs. We believe it would reduce environmental impact by reducing the size of factories. It could potentially improve the security by reducing the length of the supply chain. And we believe there would be a good business case potentially for drug firms to make to on-shore those factories and bring them back to the U.S., with the net result that we would see the additional redundancy and increased security that you are rightly asking how to incentivize.

Senator CORNYN. Thank you, Dr. Throckmorton. This is beyond the scope of really what this hearing is, but I could not pass the opportunity to ask you those questions. I appreciate your answer, and I trust that at some point the Finance Committee and the Senate and the Congress as a whole will take up how to reduce our vulnerability to the supply chains that we have seen is a risk to our public health and our ability to deal with risks like this pandemic, for the benefit of the American people.

Thank you, Mr. Chairman. I will kick it back to you.

The CHAIRMAN. Thank you very much for taking over while I voted.

I am going to start with Dr. McMeekin. The Government Accountability Office has noted that almost all domestic inspections are unannounced. However, the FDA often preannounces foreign inspections. In some cases, FDA has provided 12 weeks of notice before a foreign inspection.

Question number one: by providing advance warning, does it not give bad actors time to hide the true nature of the problems at their facilities?

Dr. MCMEEKIN. So in general, domestic surveillance inspections are almost always unannounced, whereas in foreign establishments, generally we give notice of surveillance inspections.

Given the importance of avoiding a potential refusal and waste of ORA resources, most foreign inspections are preannounced. And this preannouncement is intended to verify that the facility is indeed a drug manufacturer with the jurisdiction under the FDA. To facilitate the inspection process and ensure appropriate reference, the personnel will be made available.

We also announce foreign inspections due to the jurisdictional differences between domestic and foreign firms. The preannouncement process documents the foreign firm's agreement to allow FDA to inspect.

When a foreign firm refuses an inspection, FDA takes a different course of action than with a domestic refusal. In the domestic arena, FDA can seek an inspection warrant to enter the facility. However, in the foreign arena, due to the jurisdictional differences, FDA can refuse products at the border or not grant an approval. But FDA does not have the authority to compel the firm to allow FDA to enter and inspect.

In mid-2019, we did initiate a change to our IT system to actually record data of whether an inspection was announced or unannounced. Efforts are underway to include a data field in our inspectional database in the next version, scheduled for this June, to accurately record whether an inspection is announced or unannounced.

Having this accurate data will enable a critical evaluation of the outcome of inspections. Although typically domestic sites are not announced and foreign are typically preannounced, we do conduct for-cause inspections in the foreign arena.

The CHAIRMAN. I want all three people to answer this. Do any of you know why the Obama administration shut down the India Pilot Program?

Mr. ABDOO. Thank you, Senator Grassley, for that question. The India Pilot was not a true pilot. It was rolled out only in one country. It had no metrics by which we could evaluate whether it was a success or not. And it was collecting data with inherent bias, in that we perform unannounced inspections abroad on a for-cause basis, meaning that FDA had already determined that those firms had significant problems.

We did, however, implement some best practices that we determined were useful from the pilot program. First, we stopped having firms issue letters so that we could get visas for our investigators. Second, we stopped having firms make our hotel selections for us. And third, and probably most importantly, we began a program whereby the investigator going out on the inspection received a preapproval briefing from his colleagues or her colleagues at the ORA headquarters to improve the efficiency and effectiveness of the inspection.

The CHAIRMAN. I asked all three of you to respond to that, but because of time I want to ask Dr. Denigan-Macauley, would unannounced foreign inspections improve FDA's ability to oversee the drug supply chain? And if not, why not?

Dr. DENIGAN-MACAULEY. We do feel that unannounced inspections are very important and, as was noted, some are done, but they are very few, and it does raise questions about the equivalency to what we do here in the United States.

The CHAIRMAN. And also to you, should FDA gain visibility into the active pharmaceutical suppliers for final dosage form facilities? Would that better help FDA oversee the supply chain? And if not, why not?

Dr. DENIGAN-MACAULEY. So understanding the supply chain for the active pharmaceutical ingredients is very important. It is challenging. It is quite complex. Ingredients can come from many different sources. And being able to enhance that oversight and visibility into that supply chain would be something that would be very valuable to understanding the safety of the drug.

The CHAIRMAN. My time is up, so, Senator Wyden?

Senator WYDEN. Let me start with you, Dr. Denigan-Macauley. On March 28th of this year—so this is on the Trump administration's watch—the FDA issued an emergency use authorization allowing the acceptance and use of two malaria drugs for the treatment of COVID–19 through the stockpile. One source for these drugs which the FDA specifically allowed into the United States

was manufacturing plants in Pakistan. Rick Bright, the HHS whistleblower, reported these plants had never been inspected by the FDA.

Another source of the malaria drugs specifically allowed into the United States by the FDA was an Indian company which is on the FDA import alert list, and which has been prohibited by the FDA from bringing these exact drugs into the United States since 2015.

These are drugs that have long been known to carry cardiac health risks. There was not any solid medical evidence that they were effective in the treatment of COVID–19.

My first question to you, Dr. Denigan-Macauley, is, is it dangerous to America to import and distribute drugs from India that, up until a few days ago, could not come into our country because they were on the import alert list? I hope we could get a "yes" or "no" answer to that question.

Dr. DENIGAN-MACAULEY. Yes; we would have concerns and hope that it is a science-based decision.

Senator WYDEN. Is it dangerous to Americans to import and distribute drugs from facilities in Pakistan that have never been inspected? A "yes" or "no," please.

Dr. DENIGAN-MACAULEY. Yes; dangerous from any country not inspected.

Senator WYDEN. Dr. Rick Bright, the former head of BARDA, is now a whistleblower and has said that the FDA process for approving the drugs was not based on science, it was based on politics.

So let me ask you—because we are not going to get you into politics here—is that how the process is supposed to work? What I have described, is that the way things are supposed to traditionally play out so as to protect the public interest?

Dr. DENIGAN-MACAULEY. It should be based on science.

Senator WYDEN. No, but I just described to you the process. Is the process that I described the way things are supposed to work?

Dr. DENIGAN-MACAULEY. We have not looked extensively into that, and we have ongoing work looking at emergency use authorizations, and we would be happy to address that issue once we have looked carefully to ensure that that was the process used.

Senator WYDEN. So you are going to look at whether this process I have described sounds like the traditional process that is based on science? Because Rick Bright, the whistleblower, has said this does not resemble science, and I just asked you about whether the processes were dangerous, and you told me "yes." So it is kind of hard to see how something that is dangerous by your words is somehow in line with the process, but we will wait and see about your follow-up inquiry.

Now one of the problems created by efforts by the President to talk up the dubious nature of these malaria drugs is that it has created shortages of the drug for Americans who rely on them for illnesses unrelated to COVID–19. How can those Americans be sure that the drugs they depend on are safe, when drugs that we know are not inspected by the FDA are coming into the country?

Dr. DENIGAN-MACAULEY. So there is no country-of-origin labeling. So as a consumer, you would not know if that came from Pakistan or from an uninspected or inspected facility.

Senator WYDEN. Okay, so that is yet another factor in raising concern about how all these practices that we are talking about from March and the following weeks—on the Trump administration's watch—represent real danger, and I appreciate your laying that out. And that is why I have, frankly, already gone through it with the chairman. If you want to get stuff changed, you have to have the person here who can actually change matters. And that is why we felt so strongly about it.

One last question, if I might, for you, Dr. Denigan-Macauley. The U.S. has found itself horribly short of medical supplies. A search for N–95 respirators and PPE has been a nightmare for my State for weeks. After Oregon bought respirators that the FDA had authorized for import from China, under an emergency use authorization, the FDA then removed them from the approved list. At the same time, companies that Oregon had been trying to get EUA approval for to make respirators had been unable to do so.

How does it make sense that manufacturers of substandard equipment from China get an FDA emergency okay to ship to America, and manufacturers in the United States and my State that want to make those same products get put on hold? How does that make sense?

Dr. DENIGAN-MACAULEY. I do not have an answer for you. FDA does have oversight over these medical devices. It is a decision that FDA alone makes with that authority, and in coordination with the task force, so FEMA and DoD in support of FDA.

Senator WYDEN. I just hope we can get that changed. Because to me, it defies common sense that respirator manufacturers in China can get an emergency authorization and manufacturers in the United States cannot get a call returned. That means something is really out of whack. Again, the person who is accountable at the agency for changing the kinds of problems we have is not here. And that is why I felt so strongly about making it clear that we think we are not going to get to the bottom of it until we hear from him.

Thank you again, Mr. Chairman.

The CHAIRMAN. Thank you. The next person on a first-come-first-served basis would be Mr. Toomey. I will wait a couple of seconds.

Senator TOOMEY. Mr. Chairman, can you hear me?

The CHAIRMAN. Yes, I can hear you. Go ahead.

Senator TOOMEY. Thank you very much.

I want to go back to the line of questioning that Senator Cornyn was pursuing. Dr. Throckmorton, back in March the FDA Commissioner identified 20 drugs out of the over 20,000 drugs that are available in the United States—20 he identified as being solely made in China or containing an API that was solely sourced from China. Further, I believe that in this report it was determined that none of these drugs were considered critical drugs. And I think the criteria for being "critical" is a drug for which there is no available substitute.

So first of all, is that your understanding of the extent of dependence on China as a source of drugs and API? Because certainly that makes it sound as though there is not a great deal of reliance on Chinese sources for critical drugs. Is that your understanding?

Dr. THROCKMORTON. Senator, let me answer your question by going back to where we found ourselves in March and the situation we needed to respond to.

So, as we typically respond to an increase in need for a drug, we see drug shortages occur. When drug shortages occur, I have a staff whose sole job, 24/7, is to reach out to manufacturers, look at API manufacturers, identify possible sources for those products.

So when go back to March, what we found ourselves in was a situation where we were looking to identify the products that were essential, and which products were not as essential for the immediate response to COVID. That drug shortage team, along with other offices, went to work looking at the available products. Where were they made? What products were available?

And the shortest answer to your question is, yes, you are right. China had a small footprint as far as the creation of manufacturing of those drugs. Having——

Senator TOOMEY. Well, can I just get a clarification here, Doctor? Are you saying that this report, these 20 drugs that were identified, these are just within the universe of drugs that are for the purpose of treating COVID–19, or is it broader than that?

Dr. THROCKMORTON. A great question, and I apologize if I was not clear. Definitely broader than that. And again, it starts with where we found ourselves in March. We knew less than we do now about the impact of COVID, much less than we know now about the specific drugs that are needed. And so our focus was on products that we knew were historically in shortage, products that we anticipated were likely to be needed in hospitals.

As we learned more, we responded in——

Senator TOOMEY. Yes; my question is focusing much more broadly than just on COVID–19. I want to understand. The American public has an understandable concern about whether or not, and to what extent, we could be reliant on any one country, and most of all an adversarial country, for something as important as lifesaving medicines. But it sounds to me like, from this March report, the FDA's conclusion is that there are no drugs that are considered critical drugs—in other words, drugs for which there is no substitute—on which we rely on China, and less than one-tenth of 1 percent of all drugs are sole-sourced from China or contain an API that is solely sourced from China.

Do I have the basic facts correct?

Dr. THROCKMORTON. I will have to get back to you about the basic facts. I do not want to mislead you about that. But I do want to agree with your focus on the larger issue of total availability. Whether a product comes from a specific country or not, it is important—I am not minimizing that. But it is more important for me as a U.S. Federal drug official to make sure the drug is available from somewhere to meet the needs of the American public.

So if it is China, or it is France, or it is whatever, is of interest, but I am even more interested in knowing the total available market. Can it meet the needs of the U.S. or not? If it can, and it is done to high quality, then that is the piece that I am going to want to stay focused on.

Senator TOOMEY. So we have, certainly in my State of Pennsylvania, we have heard from health-care providers, hospitals, and

pharmacies about shortages of drugs that they wanted to be able to administer, and much of which were related to COVID treatment. It was pain medicine. It was antibiotics. It was inhalers. It was a variety of medicines. And there were shortages.

So could you characterize the source? Is it just because there was a sudden spike in demand, because suddenly we had a lot of people with COVID–19? Or were there other factors contributing to these shortages?

Dr. THROCKMORTON. That is a terrific question. The short answer is, we do not know all of the factors that led to that, whether it was distribution challenges with particular hospitals, or whether it was solely related to isolated demand in particular areas. There were different factors that drove spot shortages that were extremely serious.

So where I started before was to say, we focused on the larger market. And that has been our short goal. With COVID, we had to start worrying about your hospitals in Pennsylvania——

Senator TOOMEY. And just as my last—I am probably out of time—just a last quick, final question. Are you aware of any case where a source of these medicines from overseas, the country or the manufacturer overseas, decided for whatever reason not to distribute to the United States medicines that they normally would have? Was there a conscious decision to withhold medicines that American consumers needed?

Dr. THROCKMORTON. I am not aware of any case where the country carried through on that—that threat to withhold medicines; no.

Senator TOOMEY. Okay; thank you very much, Mr. Chairman.

The CHAIRMAN. You bet. Senator Stabenow?

Senator STABENOW. Yes; thank you very much. Thank you, Mr. Chairman and Ranking Member Wyden. And I certainly agree that the FDA should increase inspections to make sure that drugs we rely on are safe and effective.

I do think it is important to note that the current budget, that is the Trump administration budget for 2021, actually froze the number of field staff for human drug and biologic safety programs, which is of great concern to the public. And they actually called for budget cuts. So we certainly need to make sure we are not doing that.

This is obviously an important topic. At the moment, though, we are looking at over 100,000 people having lost their lives in the United States because of COVID–19, over 5,000 people in Michigan alone. And we have an urgent, urgent need to address this major health-care pandemic, and be very much focused on it. And now, on top of everything else, we have another huge urgent issue, which is what is happening in terms of African Americans in this country. And not only racial disparities on display because of COVID–19, but also what we are seeing now as a result of the horrific murder of George Floyd.

The violence to African Americans has gone on too often and for way, way too long. And it is all interconnected. The reality is that racism is a human rights issue, but it is also a health issue. And I think that is playing out in COVID–19, where 14 percent of Michiganders are African American, yet over 40 percent of the deaths are African Americans, because of health disparities. So this

is a huge issue. So we have all got to come together and bring accountability and change to the country, and I hope we will do that.

My colleagues have talked a couple of times about what we need to do in terms of bringing pharmaceutical drugs, bringing the needed medicine back to the United States. I could not agree more that we need to do that. I do want to point out, though, that in the legislation that was passed by Republicans in 2017, there were trillions of dollars in cuts and billions of dollars to the pharmaceutical industry, but nothing to incentivize or require the companies either to lower the cost of prescription drugs or to bring the jobs back and the medicines back to the United States.

In fact, the structure of the global minimum tax, the GILTI tax provision, exempts the first 10 percent of income from physical assets, factories and so on, in foreign countries, which creates an incentive to off-shore assets to increase the exemptions. So we could start by getting rid of that and then focus on what we need to do here in the United States.

Let me ask a question related to specifically the FDA, where I have great concern, and the people in Michigan do, about the politics that have been projected to the FDA.

We need the FDA to be based on science and to be making decisions that are in the best interest of all of us, our safety, and the right thing to do based on science. We all know now about the President's talking and now saying he took hydroxychloroquine. And in fact the FDA provided emergency use authorization for the drug on March 28th, and now on your website you indicate that there is no evidence the drug treats COVID–19 and in fact could actually cause loss of life. But the emergency use authorization waived the Current Good Manufacturing Practices, or they talked about today allowing the drug to be imported from uninspected foreign manufacturing facilities.

Is that correct? Just "yes" or "no"?

Dr. THROCKMORTON. I cannot answer that. I will ask my colleague, Dr. McMeekin.

Dr. MCMEEKIN. FDA has inspected manufacturers of hydroxychloroquine, and as recently as April 2020, an inspection of an alternative manufacturer was actually conducted by our local office.

Senator STABENOW. Do you share these concerns about Rick Bright, who was talking about the safety issues around this, you and your colleagues—you know, the whole question of the safety around this particular drug?

The CHAIRMAN. Can you give a short answer to that so we can go on to the next member?

Dr. MCMEEKIN. I have not had those discussions. Dr. Throckmorton?

[Pause.]

Senator STABENOW. Thank you, Mr. Chairman. I am out of time, but I would just say that people are deeply, deeply concerned. We want to be able to trust the integrity of the FDA, and with the politics and things that have been happening, it is deeply concerning.

The CHAIRMAN. Thank you. Senator Sasse is next.

[No response.]

The CHAIRMAN. Okay, then Senator Cantwell.

[No response.]

The CHAIRMAN. Okay, then Senator Menendez.

Senator MENENDEZ. Thank you, Mr. Chairman.

The CHAIRMAN. Go ahead, Senator Menendez.

Senator MENENDEZ. Thank you, Mr. Chairman.

President Trump announced last Friday that the United States would terminate its relationship with the World Health Organization, terminating our relationship with the world premier global health organization. The administration is abdicating, in my view, the U.S.'s long-held leadership role on health on the world stage, a role that China will be eager to fill. This decision also undermines the safety of Americans. We know that if we do not work in partnership with the WHO and the international community to combat COVID–19 everywhere, all Americans will remain at risk.

So, Mr. Abdoo, beyond its urgent work on COVID–19, WHO is also the central entity to the fight against other major health threats that matter to Americans. The bulk of U.S. funds to WHO helps saves lives, gives hope to populations around the world facing diseases like polio, malaria, measles, tuberculosis, HIV/AIDs, including in humanitarian hot spots like Yemen, the Democratic Republic of Congo, where agencies and NGOs are unwilling to work.

How does the administration intend to address these needs? What is the plan?

Mr. ABDOO. Thank you for that question, Senator Menendez. I am not familiar with those discussions and would refer you to the National Security Council or the presidential spokesperson.

Senator MENENDEZ. So you have no idea on these issues relating to the World Health Organization?

Mr. ABDOO. As I said, I have not been privy to those conversations.

Senator MENENDEZ. Pretty amazing.

Dr. Throckmorton, on April 8th I sent a letter with Representative Pascrell to Dr. Hahn to express concerns about the FDA's emergency use authorization approval process during the ongoing COVID–19 pandemic, and in particular the fast-tracking of approvals for potential treatments promoted by various administration officials, including the President.

The FDA is the gold standard worldwide for drug and device approval, and I believe it is important to ensure that nothing, especially pressure from the White House, erodes that public trust in the FDA.

Can you confirm for the committee that the FDA did not change its protocols for EUA approvals during this pandemic, in specific to approvals for hydroxychloroquine or chloroquine?

Dr. THROCKMORTON. Senator, I was not privy to all of the discussions that led up to the EUA authorizations. I can tell you I am aware of no instance of political influence on any of the decision-making.

Senator MENENDEZ. But the question is, did the FDA—can you confirm that the FDA did not change its protocols for EUA approvals during the pandemic?

Dr. THROCKMORTON. The approach, as far as I am aware, was the same as the approach that we have taken in past emergency use authorizations.

Senator MENENDEZ. Well then, explain to the committee how is it that the FDA issued emergency approval of hydroxychloroquine and chloroquine to treat COVID–19, despite the fact that there was no adequate and well-controlled trial demonstrating safety and efficacy for COVID–19 patients?

Dr. THROCKMORTON. I think what I would rather do is refer you to the materials that are available on our website that lay out, in general ways, the types of information that we had at the time that we approved the emergency use authorization. There were data available, and a decision was made at that period of time in support of the emergency use authorization. I should say, we continue to collect additional information, continue to reevaluate as additional data become available. That led to the drug safety communication——

Senator MENENDEZ. If you want to refer me to documents, I do not need to have a hearing. I have you at a hearing. At the end of the day, there were former FDA officials who questioned the EUA, noting the lack of scientific evidence; and sure enough, researchers are raising concerns about hydroxychloroquine. Just this week, the WHO halted its trial of hydroxychloroquine due to harmful side effects, including heart problems.

So you know, we should have Commissioner Hahn, then, come to explain this discrepancy.

Dr. Denigan-Macauley, given that we are likely to see additional global spikes in cases during the pandemic, what specific steps should the FDA take to ensure continued oversight of foreign manufacturers, and also to ensure the safety of their inspectors?

Dr. DENIGAN-MACAULEY. Thank you; yes, it is important that the inspectors have their safety taken into consideration. So I can certainly understand what FDA is doing on that end.

It is important, though, that the decisions be made on science, and that they continue to get the critical information that they need to know what establishments may be at risk. And so, for example, with the EUA, the emergency use authorization, we do have work beginning that is going to look at that, to look at the decision-making, and look to see if any criteria had changed. We have previously reported that you need to maintain criteria when you take a drastic step like that, allowing an importer who is banned to be able to have a drug like hydroxychloroquine come into the United States.

So they need to be diligent. And while we are in an emergency, they still need to be very careful in moving quickly during this unprecedented time, to ensure that they follow the steps they have put in place for the safety of our drugs.

The CHAIRMAN. Is Senator Sasse ready?

[No response.]

The CHAIRMAN. Is Senator Cantwell ready?

[No response.]

The CHAIRMAN. Okay, Senator Carper.

Senator CARPER. Senator Carper is ready.

The CHAIRMAN. Go ahead.

Senator CARPER. Mr. Chairman, thank you for the hearing, you and Senator Wyden, our ranking member. Thank you to our witnesses, especially the one who I think was an undergraduate at the

University of Delaware in animal science a few years ago. We are happy to welcome especially Mary Denigan-Macauley, and we ask you guys at GAO to pass on our sincere appreciation for the work that you do every day for our country.

Dr. DENIGAN-MACAULEY. Thank you.

Senator CARPER. You are welcome, and we thank you.

Before I ask a question or two of our witnesses, I want to make some brief comments. Racial disparities in this country of ours are rampant, and the COVID–19 pandemic is only exacerbating some of those issues, as we know.

People of color are less likely to work at jobs that would allow them to work from home. In addition to having increased exposure to the virus, people of color have lower access to health insurance, healthy foods, thus increasing the likelihood of a pre-existing health condition. These issues, paired with many others such as economic inequities, make people of color disproportionately more likely to contract COVID–19 and die from it. Nearly 23 percent of the 100,000 COVID–19 deaths in the U.S. are African Americans, while they only make up about 13 percent of the American population. Hispanics and Latinos make up 4 percent of the U.S. population, but make up 11 percent of cases.

With the recent killing of George Floyd at the hands of police officers, we are seeing yet again another form of devastating effects on communities of color, and particularly black Americans. Americans across the country are feeling deep pain and devastation, and they are grieving the loss of loved ones to COVID–19, and the loss of George Floyd. We can do better than this. We must do better than this.

The first question I have is for Mary, and I would expect the GAO—it is kind of a two-part question. Does GAO have any work examining racial and ethnic disparities in health care that would speak to important issues to consider in light of the response to COVID–19?

Dr. DENIGAN-MACAULEY. We do. We do. We have work that we will begin, looking at the disparities for COVID, specifically for the reasons that you mentioned. And it will be very important to see the results of that work.

We also issued a report recently—I believe it was in April of this year—on maternal mortality. And you see the same disparities there that we are seeing here, with Native Alaskans and Hispanics and black women dying more frequently of maternal mortality-related deaths than other ethnicities in the United States. So it is very concerning. And it is important too that, as we go forward with COVID, that we look not only at the data, but how we are collecting it, and that we look at how we are reporting it.

Because one of the findings that we made about maternal mortality was that the data that was being collected was very difficult to get—real-time data—and to get it out there in time to make it useful for the researchers. Sometimes it lagged as much as 3 years.

So during this pandemic, right now we need data more quickly than that. So hopefully the CDC, I am sure, is taking that under consideration for lessons learned going forward with COVID.

Senator CARPER. Thank you for that response. Let me ask a follow-up question. Does GAO have any work examining the collec-

tion of health-care data that raises issues important to the COVID–19 responses, based on what you just said?

Dr. DENIGAN-MACAULEY. Yes. Well, I think number one is ensuring that those data can be collected in a way that can be collated, and ensuring that the States are doing it equally. As you noted, data is collected at a local level, and then it is rolled up. And so that would be very important. Our past work has shown that it needs to be collected in a way that it can be standardized and equal across all of the States.

Senator CARPER. Thank you. And a question to be shared by Dr. McMeekin and Dr. Throckmorton. What are you and your colleagues doing to ensure that the rules of the road for COVID–19 tests and PPE manufacturers are clear and consistent and stable enough to ensure that we, as a country, can produce and procure a sufficient and high-quality supply of tests and PPE?

Dr. McMeekin?

Dr. MCMEEKIN. So we would continue with our tools to help as these products are imported in. We have additional tools to complement the inspection; we utilize and import screening tools that predict where we can adjust based upon different devices or different products. We also conduct physical examinations of product samples, and we will continue that effort.

Senator CARPER. Dr. Throckmorton, do you have anything to add?

Dr. THROCKMORTON. I do not have anything to add. The devices are regulated in a different center. Our major interactions center around the shortage groups. We have been trying to share whatever shortage information we could obtain with that group around PPE to make sure they had that.

Senator CARPER. Thank you, Mr. Chairman.

Charles Throckmorton, who was a Marine—I understand he is a Lieutenant Colonel now—was an attaché in our office for a year or two. And he is about to go back to Dover Air Force Base and is doing great work for our country. I just want to say, he reflects well on the Throckmorton family.

The CHAIRMAN. Before I call on the next Senator, without objection, I want to put in the record letters of oversight that I sent to HHS and FDA, regarding their foreign inspection regime. Those letters were sent on June the 27th, 2019. And on August the 6th, 2019, I sent a second oversight letter to HHS and FDA. We received responses to both, including thousands of pages of records, and these letters will be inserted in the record without objection.

[The letters appear in the appendix beginning on p. 74.]

The CHAIRMAN. Now I will go to Senator Sasse.

[No response.]

The CHAIRMAN. Is Senator Cantwell ready?

[No response.]

The CHAIRMAN. Then is Senator Cardin ready?

Senator CARDIN. I am here, Mr. Chairman; thank you.

The CHAIRMAN. Go ahead.

Senator CARDIN. Thank you, Mr. Chairman, and let me thank all of our witnesses. I want to ask a question to Dr. Throckmorton as it relates to the supply chain issue and the shortages of drugs.

We recognize that COVID–19 makes life more challenging in regards to the supply chain, and we want to make sure that the supply chain is safe. We also want to make sure that, to the extent possible, we have our domestic supplies and we do not have that risk factor.

But before COVID–19, we found drug shortages in the United States, not because of foreign sources, but because it just was not as profitable for drug companies to manufacture particular drugs than other drugs. And in cases where there was a single U.S. source for those drugs—and I am talking about important drugs dealing with infant safety, dealing with cancer maintenance treatments, dealing with diabetes—we had a shortage in the domestic supply because of the economics involved.

Now, we are going to do some bills to try to do something about it, but does the FDA have a strategy to make sure that we do not have drug shortages in this country? Even when there are adequate supply chain issues, it is more the economics of the private drug manufacturer deciding not to make enough of that drug available to the population.

Dr. THROCKMORTON. Senator Cardin, you raise an incredibly important point. COVID basically superimposes new demands on the drug supply on top of existing drug shortage demands.

So we started with a situation where we were challenged for many critically important drugs, and then COVID hit us. And now we have a sort of additional challenge. Yes, I believe there are things that we can do to address economic disincentives that are leading to choices made by manufacturers either to leave the market or to seek less-expensive places for manufacturing.

We put out a drug shortage report, as I know you are aware, last fall. And it laid out some of the solutions that we believe are important. One critically important one I am very fond of, that I talk about now, is the quality management maturity. The idea is that if we can find a way to improve the transparency about the quality of the drug supply chain, purchasers could make better choices about what products to choose to pay just a little bit more for to be assured that they were high-quality. Quality management maturity, we believe, would help lead the way to get that kind of transparency by, at least in part, giving us the ability to set up a rating system to identify products that were manufactured to very high quality, higher than just meeting the minimum standards, and that would allow manufacturers to advertise that they have received that rating, with the hope that they then would be paid just that little extra more so that they could make the choice to manufacture the product instead of the choice to leave the market.

As you point out, prices for generic drugs continue to fall, despite their being difficult to obtain. We need to find a way to change that economic incentive, if we can.

Senator CARDIN. I appreciate that answer, and I am all for providing financial incentives so that less-expensive drugs do not go into drug shortage. Count me as a supporter of that.

We have been talking about some of these drugs now for a couple of years, and there is still a shortage. It seems to me we may have to look for an additional supplier of that drug, in addition to the drug company that currently manufactures that product.

So I hope that we would look at broader ways, because allowing these shortages to continue in the wealthiest nation in the world is just ridiculous. And there is no supply issue. It is just price incentive to the manufacturer of the drug, and we should be able to overcome that together. I would hope that you would work with us and help us figure out a way to bring this to an end.

Dr. THROCKMORTON. I would be delighted to do that, sir.

Senator CARDIN. Thank you, Mr. Chairman.

The CHAIRMAN. You bet. And now I am going to go back to the top of the list to Senator Cantwell. And if she is not answering, Senator Brown would be next.

Senator BROWN. Thank you, Mr. Chairman.

Dr. Throckmorton, does the FDA have the authority to require mandatory recall of a prescription drug? It seems to me that mandatory recall authority could help expedite FDA's ability to pull an adulterated product or harmful drug from the market. Do you agree?

Dr. THROCKMORTON. Senator, we do not have mandatory recall authority. Having said that, the vast majority of the time when we do request a recall by a company, they do it. It is only the rare case where people have pushed back against the need for that recall. But we would be happy to talk with you about that.

Senator BROWN. Okay; we would like to pursue that. And we will follow up with congressional affairs at FDA, because we would like to work on that.

I want to raise one other issue and then make a brief statement—the issue of active pharmaceutical ingredients. Last year in front of the Energy and Commerce Committee, Dr. Woodcock testified there is a gap in FDA authority as it relates to APIs and reporting requirements when it comes to over-the-counter medications.

Dr. Throckmorton, can you speak a little more about these gaps, why they are problematic, and if the FDA is interested in working with Congress in filling these gaps in authority?

Dr. THROCKMORTON. I would be happy to talk in general terms about those gaps. I will begin by saying I think we are in very similar circumstances to where we were when Dr. Woodcock testified. So I believe the same issue still exists, which is that for those kinds of products, those APIs used for compounding and certain over-the-counter products, they can give them to Americans without inspections being required by the manufacturers.

Now, we do sometimes inspect those facilities, as you know. There are other ways for us to do that. But there is no requirement for it. We think that is a loophole. Dr. Woodcock called it a loophole. We would be happy to work with you on that.

Senator BROWN. Okay; we will pursue that.

Mr. Chairman and Ranking Member Wyden, I try not to indulge too often in the Senate's penchant for grandstanding. I try to work with colleagues in both parties, bringing substantive questions, especially in this committee. But I am astounded by the topic of this hearing.

Our country is in crisis. People are dying of a disease that continues to spread, particularly among seniors, particularly among black and brown workers who are keeping our society afloat, the

essential workers who are, frankly, expendable. They are not paid well. They are not protected in the workplace.

Black Americans continue to die at the hands of the very people who are supposed to protect them. The President refuses to lead. My Senate Republican colleagues refuse to stand up and speak out about it. We should be the people to fill that presidential void. I share this chairman's concern over the weaknesses in our drug supply chain, but we serve in the most powerful committee in the Senate.

This is the Finance Committee's first hearing since the onset of the pandemic and since the murders of Mr. Floyd and Ms. Taylor. And I said this morning in our Banking Committee hearing, not everything is about money. But that is what this committee has power over, and it can make a whole lot of difference to a whole lot of people.

We have power over unemployment insurance taxes, programs like Medicare and Medicaid, CHIP, the Affordable Care Act. We ought to be using that power to help the people who make the country work, and show Americans, all Americans, including our black and brown sisters and brothers, that their government is actually on their side.

We could be putting more money directly in those Americans' pockets, instead of trusting that it will trickle down from corporations, because, Mr. Chairman—I know Senator Wyden knows this, and I think you do, Mr. Chairman—it does not trickle down.

We can be discussing safety standards for nursing homes; 30,000 seniors have lost their lives to this illness. Thousands of workers, largely women, many people of color, are putting their own health care at risk for loved ones, and we are doing a hearing on this instead?

Instead, Chairman Grassley has chosen to hold a hearing on a topic outside our jurisdiction and unrelated to this crisis. Simply, Mr. Chairman, putting COVID–19 in the name of the hearing does not make it about the pandemic. This hearing is sadly no exception. It is time to step in. If you believe as I do, in the capacity of this country to meet a challenge, to continually build, to continually bend the arc a little further toward justice, we should be doing the work.

Thank you, Mr. Chairman.

The CHAIRMAN. The only disagreement I would have with Senator Brown is the fact that this committee spends tens of billions of dollars on Medicare, Medicaid, and prescription drugs. We ought to be buying quality drugs. We have jurisdiction over trade, and we ought to make sure that what enters the United States is a quality product.

So, obviously this committee has great concern about FDA's inspections overseas. And when it comes to everything else he mentioned about COVID, this committee has done several things by increasing reimbursement for Medicaid connected with COVID–19 by 20 percent, more money for Medicaid. We have put $175 million into hospitals as a result of it.

We have given out $300 billion in increased unemployment compensation. We have reduced payroll taxes for 1 year for companies that need more liquidity. We have set up a program for increased

liquidity for other companies as well, besides small businesses. And this committee has been very active in the $3 trillion that is already out for the pandemic and the shutdown of the economy and the opening up of the economy as a result of the government shutting it down.

So I think this committee has been very active in everything related to the pandemic, and we will be more active. As we decided 7 weeks ago—whatever decision we were making 7 weeks ago, we did not know if the economy would turn around. We did not know the condition of the pandemic. And we went into it with open eyes that, if there was more that needed to be done, we would do it. And we are in the middle of that process now. And when we get to the point of making that add-on decision, whatever needs to be done, this committee will be active at that particular time.

But we have billions of dollars in the CARES Act 1 that is still not out. Our work in the first step is not done yet. I will——

Senator BROWN. Mr. Chairman, if I could take the last part of my time. Lincoln used to tell his White House staff, "I've got to go out and get my public opinion bath." And I think if any of us are on the phone—I know a lot of us are on the phone a lot of the time—we still see the pain and the suffering. And I see my colleagues from New Hampshire, Oregon, and Pennsylvania, and I know how hard they work and how they are hearing about that pain and suffering. And this committee has got to be talking about extending the unemployment benefits. It has got to be talking about Medicare and Medicaid, and not having no hearings for the last, I do not know, 7, or 8, or 10 weeks, when there is so much suffering out there and so much work to be done. But I will stop there. Thank you, Mr. Chairman.

The CHAIRMAN. I know you are the person who always wants the last word, so to get on with this hearing, I will let you get away with what you always get away with.

Senator Casey?

Senator CASEY. Mr. Chairman, thanks very much for this hearing. I want to note that these issues that relate to the FDA are very important, but I do not think we can forget at this time in our Nation's history, especially this week after what happened just a week ago, I do not think we can fail to remember the murder of George Floyd and all the pain, the trauma, the anger, and the protests that have resulted from that death.

We cannot simply condemn the actions that killed him and lament the failures of our criminal justice system as it relates to the African American community. We should do both, but that is not enough. We must act legislatively.

This committee does not have the same jurisdiction as the Judiciary Committee, but this Finance Committee does have jurisdiction over health care and economic security, for example. And there is a lot we could do to examine a whole range of issues under those broad topics that relate to communities of color. And part of our set of actions to help these communities must focus on those actions.

Second, I would note that in the broad category of COVID–19—the deaths that have resulted and the number of cases—the death number is disproportionately higher for African Americans. In some States, it is more than double or triple the percent of the pop-

ulation; the percent of the deaths are outpacing by a long shot the percent of the population.

As it relates to what this committee can be doing in connection to COVID–19, one of the areas that Senator Brown mentioned would be in the area of nursing homes. We should have a hearing on nursing homes. It should focus on a couple of topics. First and foremost, we should hear from the Centers for Medicare and Medicaid Services to ask them questions, to ask Administrator Verma questions about transparency, and why information and data about cases in nursing homes and deaths in nursing homes have not been on the public record to the extent that I and Senator Wyden and a number of our colleagues have asked for.

We have had 40,000-plus deaths in nursing homes—40,000-plus, when you include nursing home residents and workers. There has been a failure to collect data. Nursing homes need a lot of things right now. They need funding, a lot more of it. They need testing. They need personal protective equipment.

I have a bill to do all of that, Senate bill 3768. It is the only bill in the Senate that would provide that kind of help, $20 billion to help States with cohorting, where they separate the residents with COVID–19 from those who do not have it, and pay for surge teams and other best practices to get the professional help that is needed sometimes when a nursing home is in crisis.

With that as a long predicate, Dr. Denigan-Macauley, the GAO did an analysis of detection, prevention, and control problems in nursing homes. Could you quickly summarize that report?

Dr. DENIGAN-MACAULEY. Yes, thank you. We did that. We looked at data from 2013 to 2017, and we found that nursing homes have widespread problems. Over 82 percent had deficiencies, and in some cases more than half of them had more than one deficiency. And it was basic infection control problems; for example, staff not washing their hands, or not disinfecting equipment, and sharing of bathrooms. And that is pretty dramatic if you are looking at now. If we were to go back in and look at that during COVID, and the infectious rate of that disease, it would be pretty devastating.

Senator CASEY. Thanks very much, Doctor.

Mr. Chairman, that concludes well short of my time, and I want to say two things. Number one is, I will submit questions for the record for Dr. Throckmorton. And, Mr. Chairman, I will say this about your leadership and this hearing. I may disagree that we should be covering some other topics, but at least you are having a hearing that relates to COVID–19, unlike what has happened on the floor the entire month of May. All nominations. Nothing on COVID–19, with the limited exception of a few votes on the Foreign Intelligence Surveillance Act.

Mr. Chairman, I will yield the balance of my time.

The CHAIRMAN. Senator Warner?

[No response.]

The CHAIRMAN. Senator Whitehouse?

Senator WARNER. Hold on; I am here, Mr. Chairman.

The CHAIRMAN. Senator Warner, go ahead.

Senator WARNER. All right; thank you, Mr. Chairman. I appreciate it.

I want to talk to the panel, Dr. Denigan-Macauley and our friends from the FDA, about supply chain issues that I think this virus has exposed. It would seem to me that our national strategic stockpile was significantly underprepared for this virus, and I guess what I want to start with today is, what kind of partnerships has the FDA looked at, particularly with outreach to both our Energy and DoD partners and your intel partners—I am the vice chairman of the Intelligence Committee—on how we would be better prepared in terms of the strategic stockpile in any future problems? Do you support any kind of partnerships there? I am not sure which of the FDA colleagues will address that.

Dr. THROCKMORTON. Senator, this is Doug Throckmorton. I can start, and the others might chime in if they have anything additional. I can tell you about the interagency partnerships that we have formed, because I agree they are absolutely critical for the response to COVID.

So we have been engaged in discussions with FEMA, for instance, from really Day One in terms of the response to the COVID outbreak, about distribution, giving them whatever information we can to help them make good decisions. I know that engages with the strategic national stockpile.

That is also focused through the Health and Human Services administration through the ASPRs—that is the name of the group there. We have also been engaged with them, again on, roughly speaking, a daily basis because we understood the need for us to provide whatever support we could for the decisions they were making about the strategic national stockpile.

Similarly, we have been in close contact with the DEA regarding controlled substances and the need for controlled substances. As I am sure you no doubt know, there have been extensive needs for fentanyl and other opioids for pain and for ventilator settings and things, and we have had to do everything we could to support that work that they do regarding the availability of those products.

And then finally, BARDA, the acquisitions group, is engaged with us around the work that Flo and other manufacturers have recently taken up——

Senator WARNER. If I could interrupt for a second; I do not have that much time.

One of the things that we have discovered, as the administration basically had States versus States searching for PPE and for testing equipment, is that a lot of that came from foreign sources, China in particular, you know. In terms of thinking this through, have you had any kind of outreach to the intel community or the defense community about how we better prepare in the future? I think there are a lot of us on both sides of the aisle who do not want to be reliant on China for APIs going forward, or on circumstances of not having a domestic supply of PPE, testing equipment—and you are talking mostly domestic agencies. What about our intel community or DoD?

Dr. THROCKMORTON. I have not been part of those conversations. That does not mean that they have not occurred, sir. I would be happy to get back with whatever information we can.

Senator WARNER. Dr. Denigan-Macauley, did you have any comment there? Did you want to speak to advanced manufacturing fa-

cilities? I think there is someone on the second panel who will highlight some of the work that is being done at Virginia Commonwealth University on advanced manufacturing in this space around APIs, but I am really concerned about the domestic sourcing of these materials.

Dr. DENIGAN-MACAULEY. Yes. And GAO has work that we have ongoing, looking at not only the strategic national stockpile, but we are anxious to be able to get out of our homes and talk to the intel communities that you are referring to, because they are key with respect to analysis and understanding of how best to ensure that those supplies are there.

We have a robust body of work looking at APIs, where they are coming from, how we are going to stockpile, medical countermeasures, the whole shebang. We will continue to report out through the CARES report every 60 days, as well as CARES reports over the longer period of time.

Senator WARNER. We are about out of time, but I do hope that we will have that resilient domestic supply chain, recognizing where we are sourcing a lot of this material and looking at this from a national security standpoint. I will tell you, Mr. Chairman, I know that, for example—Senator Wyden and I both are on Intel, and I think this is a national security issue that needs serious attention, and I hope the committee will come back and revisit it.

I yield back my last seconds.

The CHAIRMAN. Okay. Senator Whitehouse?

[No response.]

The CHAIRMAN. Senator Hassan?

Senator HASSAN. I am right here, Mr. Chairman.

The CHAIRMAN. Go ahead, Senator Hassan.

Senator HASSAN. Thank you, Mr. Chair, and thank you, Ranking Member Wyden, for this hearing. And thank you to our participants, our witnesses who are participating today.

I just want to start out by saying that I share the concerns that my colleagues have expressed, that this hearing is the first hearing that the committee has had since the onset of the pandemic. It is especially troubling, given the pain that millions of Americans are feeling at this moment in time. The murder of George Floyd happened at a time when many African Americans already were feeling despair about the way this pandemic has disproportionately taken their lives and livelihoods.

We could be working today on actions that would be constructive steps towards addressing their rightful concerns. But we are having this hearing today—and I do want to focus on the fact that in the last few months FDA has authorized the use of hydroxychloroquine for COVID–19 without properly evaluating its safety or effectiveness, and allowed highly inaccurate COVID–19 tests to enter the market.

These decisions have negatively impacted our day-to-day response to this pandemic and potentially put lives at risk, yet we do not have an FDA official here who can speak to those decisions. Moving forward, I hope this committee can conduct the type of broad oversight of the Federal response to COVID–19 that the American people deserve, including an examination of what has happened in our country's nursing homes.

Like so many other States, my State's nursing homes have been devastated, and the deaths in New Hampshire due to COVID–19 are unbelievably, disproportionately happening in our long-term care facilities.

So, Dr. Denigan-Macauley, a couple of questions for you. Your testimony before the House Energy and Commerce Committee in December touched on many of the shortcomings of FDA's foreign inspection process. Can you discuss the potential risks these shortcomings pose to Americans who rely on these pharmaceuticals, and how FDA's decision to modify its approach to foreign inspections during the COVID–19 pandemic may exacerbate those risks?

Dr. DENIGAN-MACAULEY. The GAO has reported that, while FDA has many tools at its disposal to ensure the safety of our drug supply, inspections are absolutely critical. And they stood up the FDA overseas offices specifically to be able to have boots on the ground, to be able to get the intel to find out which establishments are good or might be bad actors and to be able to get in there and to do inspections with very little notice, like we have here in the United States, to make sure that it is equivalent.

So the fact that it stopped—I understand the need for being able to protect their own people, but it is concerning. And I would want to ensure that the other steps that they have in place are rigorous.

Senator HASSAN. Well, I thank you for that clear response, because, while I too understand the need to protect FDA inspectors, their work is essential. And given the risk to patient safety, I believe the FDA's decision to curtail inspections is inappropriate. And it sounds to me, given your answer, that you have deep concerns about it too.

Dr. DENIGAN-MACAULEY. We do have concerns, and we continue our work in this area.

Senator HASSAN. Thank you.

To Doctors McMeekin and Throckmorton, last year I had the opportunity to travel to China and speak with both U.S. and Chinese officials about the massive production of fentanyl, 90 percent of which originates in China and is not regulated. I have continued to push efforts around putting a stop to illegal production and distribution of fentanyl devastating people in New Hampshire and beyond.

Doctors McMeekin and Throckmorton, can you speak to what steps FDA is taking to combat illegal fentanyl from China? I would also be interested in hearing about the work your agency is doing in China, as well as efforts to stop illegal fentanyl from crossing our border, including sales on the dark web.

Dr. MCMEEKIN. Thank you very much. Our enforcement efforts are primarily focused at our ports of entry and the international mail facilities. In addition, our Office of Criminal Investigations and our health fraud staff are investigating online sales of opioids, including fentanyl. In the States, we are working primarily on counterfeits, and also working in conjunction with other law enforcement counterparts.

In fiscal year 2019, we had 55 arrests and 53 convictions related to these products, or involving elicit opioids. So we continue to work hard on our web and health fraud activities surrounding these products.

Senator HASSAN. Thank you. Dr. Throckmorton?

Dr. THROCKMORTON. I do not have a lot to add to that. I am glad that she made the distinction between elicit fentanyl manufacturing, which is going to elicit drug use, from prescription fentanyl manufacturing, which is occurring, obviously, within the U.S. borders, because I think there has been some confusion there.

In regard to the elicit fentanyl manufacturing, we have been focusing our efforts especially at the borders, and especially online sales, working with the online sellers, the Amazons of the world, to try to stop people from being able to order elicit opioids like fentanyls on the dark web, or from other sources. I think that is a really strong focus of that.

Senator HASSAN. So, thank you. And thank you, Mr. Chair. I do not want to lose sight of the fact that, while we have the pandemic of COVID–19, we continue to have an opioid epidemic. Thank you.

The CHAIRMAN. Thank you. And now, is Senator Whitehouse available?

[No response.]

The CHAIRMAN. Okay; then is Senator Cassidy available?

Senator CASSIDY. Senator Cassidy is here.

The CHAIRMAN. Go ahead, Senator Cassidy.

Senator CASSIDY. Great; thank you. I am sorry I am not on video.

Doctor—I think this is for the FDA—Senator Toomey had mentioned about API coming from China. Dr. Throckmorton pointed out there does not seem to be that much of a shortage. But API is different than the chemicals that go within it. And it is my understanding that a greater percentage of the chemicals used to make API are coming from China. Is that correct?

Dr. THROCKMORTON. This is Dr. Throckmorton. I am not familiar with those data. We know substantially less about the sources of those products than we do about API and, as I think was mentioned earlier, we know less about API and its manufacturing and distribution than we do about finished dosage forms.

Senator CASSIDY. I will ask Mr. Abdoo, because he is involved with trade. Mr. Abdoo, are you familiar with the percentage of starting materials or fine chemicals coming from China?

Mr. ABDOO. I am not familiar with that data, but we can look into it and get back to you.

Senator CASSIDY. That actually seems to be the critical thing here, because API is one step, but the chemicals are another. And so that actually seems to be our point of vulnerability unless we have a stockpile thereof.

For example, is the high percentage of production in China of starting materials? Because it is my understanding that there is a higher percent of starting materials produced in China. What would be the reason for that? Is it cost, or is it access to a base mineral, or some other issue? It does not sound like you all are familiar with this, but I would ask you to get back to us regarding that.

I think GAO, though, has made a point that, even in normal times, it is difficult to get a clear line of sight into Chinese manufacturing. So just to say, I do think it is important for us to consider establishing a strategic API or starting material reserve.

Let me go on to you, Mr. Abdoo. Brazil and Mexico both have a presence in U.S. pharmaceuticals. Clearly, if there is geopolitical tension, it is probably better to have pharmaceutical manufacturing in Mexico and Brazil than in China, for a variety of reasons. Can you give me a sense of the challenges for pharmaceuticals in Mexico and Brazil? And how is the foreign drug inspection process going there? And would that be an alternative for us?

Mr. ABDOO. I do not have data on that at the moment, but again, I can look into it and get back to you. Regardless, our inspection protocols remain the same globally, and we hold foreign and domestic manufacturers to the same standards.

Senator CASSIDY. Let me finish with this. Dr. McMeekin, you went through a kind of elaborate why we cannot do inspections as we normally would in foreign countries, in terms of it is jurisdictional and therefore we have to notify them. There are two things about that.

In a response right after that, Mr. Abdoo suggested that we, when we were doing this in 2015, we indeed were doing inspections but that there was a bias about how these companies were selected, and that bias therefore may have biased the results. But the point was, we were doing spot inspections.

And secondly, the FDA has the ability to say, "If you do not let us in, your goods are not coming to the United States." And so, give me a sense of why your response to jurisdictional issues is different than what Mr. Abdoo said. And then also, why can't FDA just demand to be let in or else we are not letting your product come over?

Dr. MCMEEKIN. Thank you very much. Actually, you are correct. If we go to inspect a foreign facility and they refuse our inspection, we do have the authority and have used the authority to put the firm and those products on import alert, which would prevent those products from entering U.S. commerce.

And just so folks know, we do have unannounced inspections. In a foreign space, they are generally on for-cause basis. When there is a reason that is identified, such as an informant, or there is a trade complaint, we will go in and conduct an inspection. We have, and we do, conduct unannounced inspections in the foreign space.

And again, if they deny an inspection, we do have authority to place the facility, along with the products, on the import alert.

Senator CASSIDY. How many unannounced inspections did FDA do on manufacturing plants in China and India last year?

Dr. MCMEEKIN. Predominantly, they were announced. I do not have the exact figures. Remember that we do not—we are just implementing in our IT system the capability to record whether an inspection has been announced or unannounced. So once we have that data, we will be able to identify what those inspections are.

Senator CASSIDY. I am a little bit surprised that you do not have a list of how many, but I will yield back in the interest of time.

Thank you, Mr. Chairman.

The CHAIRMAN. Senator Thune?

Senator THUNE. Thank you, Mr. Chairman. And thanks to our witnesses for being here today.

Ensuring the safety and quality of our Nation's supply of prescription drugs is a key priority in the Nation's work to respond to the coronavirus pandemic and the issue of the supply chain for

both prescription drugs and PPE that has been brought to the forefront, and so I appreciate the discussion today.

To Dr. Throckmorton, as we continue discussions on the coronavirus response efforts, what updates can the FDA provide with respect to provisions needed to address supply chain issues, namely, requirements for greater transparency regarding supply chain disruptions?

Dr. THROCKMORTON. Thank you, Senator. I appreciate that question. One, I would say in general we are very grateful for the provisions that we got in the legislation. We are in the process of implementing the legislation. As you likely know, it implements in September. And so we anticipate that we are going to be able to make use of the legislative authorities that were granted in CARES to expand the amount of information that we get, and information is power in this setting, as we have discussed throughout this hearing. The more we know about products moving in the manufacturing chain, the better we can do as far as preventing shortages, or anticipating spot needs, or something like that.

So CARES is a very important piece for us, and I am looking forward to being able to come back and give you an update on exactly what we were able to do with it. But we have every expectation that it is going to be really helpful.

Senator THUNE. Okay.

Dr. Denigan-Macauley, are you aware of that provision in the CARES Act?

Dr. DENIGAN-MACAULEY. I am, but I do not have any further information.

Senator THUNE. Okay. So, just as sort of a follow-up to some of the lines of questions—and I am sure much of this ground has been covered already—but the perception has been through the course of the pandemic that there have been these shortages, or disruptions in the supply chain, particularly with regard to pharmaceuticals and PPE, as relates to those that are manufactured in, particularly China, but other places around the world.

So I am wondering if you all could just comment about the accuracy of those reports, and whether or not in fact the concerns that people have about the future with respect to those supply chains are valid, and whether or not we ought to be providing incentives to bring many of those capabilities back here and to stand up those capabilities in the United States. How reliable are these supply chains with the manufacturers that are operating currently in foreign countries?

Dr. Throckmorton?

Dr. THROCKMORTON. Yes, I might start, Senator, if that is all right. Without any question, COVID is an unprecedented demand on our drug supply chain. It is layered on top of the problem with regards to drug shortages, one that we have been working to confront for several years.

But superimposed on that were unprecedented needs for medicines. And that has required that the FDA change our approaches, create new structures to identify and respond quickly to those drug shortages when they occur, whether it's propofol in the hospitals in the New York State area, or it is some other medicine.

We have had to adapt our procedures to put in place ways to respond quickly, within hours, wherever we can to find new sources of product for the population, whether it is in a State or even in the smaller localities.

Going forward, we've got to think about the next challenge. So COVID will not be the last time we are asked to respond to a natural emergency, or an emergency of this size. And so we need to find ways to strengthen the supply chain, find ways to incentivize a supply chain that is robust and reliable, and bring things into the U.S. as a way to address that. And we are firmly supportive of things like advanced manufacturing, because the U.S. has the advantage in those areas, an advantage that could well help to steer firms onto the U.S. shore, helping all of us both with regards to security, availability, and quality for medicines that we need now, and medicines we are likely going to need for the next emergency.

Senator THUNE. Okay. Mr. Chairman, my time has expired. Thank you.

The CHAIRMAN. The next person is Senator Daines.

[No response.]

The CHAIRMAN. If Senator Daines does not speak up, I will call on Senator Young.

[No response.]

The CHAIRMAN. If Senator Young does not speak up, I will call on September Crapo.

[No response.]

The CHAIRMAN. Then the next one is Senator Cortez Masto.

Senator CORTEZ MASTO. Thank you, Mr. Chairman. Thank you, everyone, for the conversation today. Let me just say that I am from a State that seems to be experiencing enormous impact of COVID–19 that is devastating our economy. I too would ask that the chair consider having a further oversight hearing that pertains to our nursing homes. Our nursing homes in Nevada have been ravaged by COVID–19 as well, and I think at this point, I'd like to follow up on this area and many others.

So I would just put that in and echo the request from some of my colleagues as well.

Let me start with Mr. Abdoo. As we look ahead to the development of mass production of a COVID–19 vaccine, how does the agency expect to balance the efforts to gear up production quickly with the need for the oversight of these manufacturing facilities?

Mr. ABDOO. So, thank you, Senator, for that question. As you know, vaccines are regulated through our Center for Biologics Evaluation and Research, and our experts there would be the best situated to get you that information. I am happy to bring the question back to them.

Senator CORTEZ MASTO. Thank you. I appreciate that. I think that is going to be very helpful for us in planning for the future.

Let me ask you this. And also I appreciate Senator Cassidy's line of questioning, because I too have questions. I have read through the GAO report about these unannounced inspections and announced inspections. So whatever information you can provide as a follow-up, please provide it to my office.

It is my understanding after reading the GAO report that most of the unannounced inspections—when we are talking about unan-

nounced inspections, it is giving them 12 weeks or more that you were going to be presenting to their facility? Is that correct? So they have enough time to prepare for knowing that an inspection is going to occur? Is that correct?

Dr. MCMEEKIN. Thank you for the question. It is not a matter of giving them enough time to prepare. It is really having enough time for us to prepare to make sure that we have the visas available, and that our staff have actually been able to take the State Department clearance training. A foreign inspection requires more time to plan, and investigators must complete the necessary documentation for obtaining official passports, visas, and complete required State Department training. Any delays in this can actually put it in jeopardy, or require a last-minute change in travel.

Senator CORTEZ MASTO. Can I ask—and I appreciate that; it is very helpful. But by giving them advance notice of your coming, do you have concerns that they are going to take action in response to that notice? And what type of action would you have concerns that the facility would be taking?

Dr. MCMEEKIN. Again, remember that the firms, the foreign and the domestic firms, are inspected the exact same way, using the same standards and requirements, whether they are domestic or foreign.

So the expectation is for the firms to be able to have quality products developed at any time during that process.

Senator CORTEZ MASTO. Right. So what is your distinction between then a spot inspection versus an unannounced inspection? To me, there are concerns that something is going on there and you do not want them to correct it just while you are there inspecting, and then go back to that practice.

Dr. MCMEEKIN. The firms have a responsibility to have processes in place so that they can develop quality products. The inspection is one—it is a moment in time. So they have to have the quality systems in place throughout the life cycle of the product. It is not just, you know, while we are there.

But while we are there, we are looking at these quality systems. But it is up to the individual facilities and manufacturers to have a role and an ownership in making and providing quality products.

Senator CORTEZ MASTO. So then why have an unannounced inspection?

Dr. MCMEEKIN. The unannounced inspections, think of—so if we are going to do a preapproval inspection, something that is tied to the application, it is important that we do give notice on those preapproval inspections because we want to make sure that they have the data available, that we have the people to talk to at the firm who can talk to the types of processes that they have, or the manufacturing capabilities so that we can talk with them to see how they are prepared to manufacture the product that is associated with the application. So that is what we do with a preapproval inspection. So we do announce that.

And then we will not announce if we have concerns that there might be issues that have been brought to our attention from manufacturing, or if there have been patient complaints, or consumer complaints, or manufacturing complaints. We will want to go in there unannounced.

Senator CORTEZ MASTO. And why would you want to go in unannounced?

Dr. MCMEEKIN. You know, sometimes just to not give them any specific insight, primarily.

Senator CORTEZ MASTO. Because you have concerns that they might do something in response to the notice that you are coming?

Dr. MCMEEKIN. There may be some, but what we have seen from our outcomes is that in general there is not a huge difference when we have an announced inspection or we do not. If we look at our "official action indicated" where there have been violations, from our domestic standpoint that is at about 7 percent for drug products versus in the foreign arena, that is more about 10 percent.

Senator CORTEZ MASTO. Thank you. I notice my time is up. Thank you. It looks like I have gone over. I appreciate the indulgence.

Senator DAINES [presiding]. Thank you.

Well, I guess I will wrap up here with this first panel, and I want to thank you for coming to the committee today and providing your perspective and expertise on this very important topic.

China's cover-up and their response to the coronavirus outbreak set the world behind and caused this pandemic to rage across the globe and devastate the economies and public health. The Chinese Community Party's reckless actions to downplay and lie about the severity of this virus has changed the lives of every American.

Montanans across our State are losing their jobs. Businesses are closing their doors. Working moms and dads are struggling to put food on the table. As more information comes to light on the deadly Chinese cover-up of this virus, we must hold China accountable to ensure this never happens again.

It is long overdue to end our reliance on China to produce medical supply equipment like PPE, as well as life-saving drugs. Over 70 percent of personal protective equipment and over one-third of our antibiotics are imported from China. Being dependent on China is a threat to our national health and our national security. America will be safer, and America will be stronger when we bring our pharmaceutical and medical manufacturing supply chains and those jobs back to America.

Commissioner Abdoo, there are substantial concerns that China's pharmaceutical industry is not effectively regulated by its government. China's regulatory apparatus is inadequately resourced to oversee thousands of Chinese drug manufacturers even if Beijing made such oversight a greater priority. This has resulted in significant drug safety scandals. What are the most challenging aspects of maintaining quality control of Chinese pharmaceutical imports into the United States?

Mr. ABDOO. Thank you for that question, Senator, and I will start off and then turn to my colleagues. Through our office in Beijing, we work extensively with the National Medical Products Administration in China to raise the standard of their ability to regulate products within their jurisdiction.

We do this by recommending harmonization with international standards, by promoting membership in pharmaceutical inspection cooperative schemes, which help create standards for inspections, and we do this also in addition to work with the FDA through edu-

cating the industry about requirements for FDA so that they can better comply and improve the quality of the product that they are exporting to the United States.

With regard to what we do here domestically in terms of importation and so forth, I am going to turn to Dr. McMeekin.

Dr. MCMEEKIN. So, as Mr. Abdoo mentioned, FDA's jurisdiction over foreign firms' products begins when the products arrive at our borders and attempt to enter into interstate commerce.

And so FDA uses additional tools to complement those inspections. And this includes utilizing our import screening tool called PREDICT, and we can and have adjusted that accordingly. We also conduct physical examinations and/or product testing at the borders to make sure of that as products come in.

We are also requesting—we can request records from some facilities. So we can request records; we have received authority to request records in advance so that evidence inspections are actually in lieu of inspection. So we are collecting these to look at batch records, program data, to be able to see if they are complying with GMPs.

Thank you.

Senator DAINES. Yes; so you are not actually monitoring the process of operations in the plant for GMPs? You are looking at documentation but not actually having any physical presence on their site?

Dr. MCMEEKIN. During the pandemic.

Senator DAINES. Okay. And a follow-up question, back to the Commissioner: what are the biggest impediments to drug manufacturing in America? And what would be the benefits of having a stable domestic supply chain for our most critical drugs?

Mr. ABDOO. Thanks for the question, Senator. I think Dr. Throckmorton might be in a better position to talk about drug manufacturing in the United States.

Dr. THROCKMORTON. Thank you, Senator. When we talked before about this, we identified a few factors. One obviously is labor costs. Another factor relates to the environmental regulations. In parts of the world, there obviously are very different standards in that regard. And third is the economics of drug manufacturing.

So, if you look back at the drug shortage report that we created last fall, we believe there is fundamentally a disconnect in terms of the incentives to create high quality, and the reimbursements for the products that are of high quality. And we think we can change that if we could provide additional transparency, potentially grading, identifying products that are made to a very high quality, and make those known to the American public so that buyers would know that they could potentially choose those products over products that barely meet the mark. And we would be very happy to talk to you about the ideas we have along those lines.

Senator DAINES. Thank you. I am out of time as well, and so this will conclude our first panel. I want to thank our witnesses for being here today and sharing their very insightful testimony in answering these questions.

With that, we are now ready to seat panel two.

[Pause.]

Senator DAINES. Okay. We'll get started with the second panel. I'd like to start with the introduction of, first of all, David Light.

David is a biotech entrepreneur and scientist with over 10 years' experience in the field. He is the founder and CEO of Valisure. Valisure tests its drugs for toxins, carcinogens, and dilution rate before dispensing to patients. David helped found, fund, and invent the core technology at Valisure and is named inventor on numerous patents.

Our second member of the panel today is Martin VanTrieste, who is president and CEO of Civica, Inc. Civica, Inc. is a nonprofit, non-stock corporation founded in 2018 and is part of a new U.S. Government-funded partnership to produce essential generic medicines and their ingredients in the U.S.

The immediate priority for the partnership will be a COVID–19 response. Today over 50 health systems are Civica members, representing more than 1,200 U.S. hospitals and over 30 percent of all licensed U.S. hospital beds. Since we do not have time restraints, each witness has 5 minutes for their opening statement, and we will begin with Mr. Light.

STATEMENT OF DAVID LIGHT, FOUNDER AND CEO, VALISURE, NEW HAVEN, CT

Mr. LIGHT. Chairman Grassley, Ranking Member Wyden, and members of the committee, thank you for the honor of being able to speak before you today. I am the founder and CEO of Valisure, where our mission is to help ensure the safety, quality, and transparency of medications, and we do this with a very simple but novel approach: we check. Valisure is the only pharmacy that checks the chemistry of every batch of every medication at no additional cost to patients. This is particularly important, given our Nation's heavy reliance on overseas manufacturing and COVID–19 putting additional strain on an already stressed system.

Valisure currently rejects over 10 percent of the medication batches we test due to a variety of product defects. The pharmaceutical supply chain is extremely complex and heavily reliant on the self-regulation of overseas manufacturers. When you buy a bottle of medication, it is like buying a used car. Those pills are often already a year or two old, have traveled thousands of miles and touched dozens of hands. No one buying a used car is satisfied to know that the original manufacturer said, "It's good." You want a CARFAX report. You want to see a 100-point inspection on that car. None of that transparency is available for medications.

While the FDA cannot do everything or be everywhere, we strongly believe that more can and must be done. The idea of independently checking drugs may be new to industry, but not to the academic world. However, warnings from academics have unfortunately been largely ignored. A grim example of this is the drug Zantac. In 1977, Senators sat in this very building and listened to testimony that certain drugs are unstable and form the extremely potent carcinogen NDMA.

Similar concerns were raised a year later at a summit held by the World Health Organization and the United Nations. Zantac has the exact chemical structure to form NDMA that the scientific community warned about, and yet the drug was approved only a few

years later. In the following decade, dozens of studies implicated Zantac as chemically unstable and easily prone to forming NDMA, but these papers had practically zero impact. By the 1990s, Zantac had become the top-selling drug globally and among the most commonly prescribed to treat acid reflux in pregnant women and infants.

It was not until 2019, 36 years after the drug's approval, that Valisure performed the simple action of independently checking generic Zantac syrup prescribed to our co-founder's infant daughter. The results were so dramatic we immediately took the drug off our formulary. But we were not satisfied by simply publishing our findings in a journal.

We petitioned the FDA directly. We spoke to the press. We did not back down from the crystal-clear science that Zantac is fundamentally unstable and should be taken off the market. Two months ago, after dozens of countries had already banned this dangerous drug, the FDA finally granted our petition, and Zantac was officially taken off the U.S. market.

Without independent testing and the drive to make it broadly transparent, Zantac would have remained on the market for many more decades to come. The immense value of independent testing does not have to be limited just to Valisure's pharmacy.

I believe there are two clear paths to applying independent analysis throughout the U.S. First is a data-driven approach: drug quality scores. Results from independent chemical analysis can be combined with broad regulatory data and boiled down into quality scores that can be as simple as a red, yellow, green rating that provides transparency to any drug purchaser. Buyers can use this guidance to buy green, occasionally yellow, and avoid red. A landmark paper by leaders from eight prominent health-care institutions was just published on this approach last week.

Additionally, for a handful of important drugs that are particularly vulnerable to quality issues, there is a more definitive solution: what we call "certified drugs." By employing independent batch testing of drugs up to the manufacturer level, we can weed out poor-quality batches and bring certified medications to millions of Americans regardless of which pharmacy they go to.

This is entirely reasonable to do for critical drugs such as metformin. Metformin is the top diabetes drug and the fourth most prescribed medication in the U.S., with over 80 million prescriptions a year. Valisure has published two studies showing that approximately 40 percent of metformin products are contaminated with the carcinogen NDMA above FDA acceptable limits. This means millions of Americans are taking a drug every day that contains a carcinogen that absolutely should not be there.

In summary, we have very serious problems in the drug supply chain that are caused by a very complex set of factors, all of which are made worse by COVID–19. It is imperative that we act quickly to better protect the American public. And above all, independent scientific analysis cannot continue to be ignored and must be a part of a new, transparent path forward.

Thank you very much, and I look forward to your questions.

[The prepared statement of Mr. Light appears in the appendix.]

The CHAIRMAN. We will now go to Martin Van Trieste.

STATEMENT OF MARTIN VanTRIESTE, RPh,
PRESIDENT AND CEO, CIVICA, INC., LEHI, UT

Mr. VANTRIESTE. Thank you, Chairman Grassley, Ranking Member Wyden, and members of the committee. I am Martin VanTrieste, the CEO of Civica. I am honored to be here and to follow a group of dedicated public servants. Civica is a nonprofit 501(c)(4) established by health systems and philanthropies to reduce chronic drug shortages in the United States. Our mission is to serve patients by making quality medications that are always available and affordable. More than 1,200 U.S. hospitals and 50 U.S. health systems have joined Civica. We also supply the Veterans Administration, Department of Defense, as well as 340B-eligible hospitals.

Many of our drugs are used in the management of COVID, and we have been able to supply them without fail. We even contributed 1.6 million vials of medication to the strategic national stockpile. Several features of the Civica model may offer insights into the broader supply chain.

We rely on long-term take-or-pay contracts to provide the certainty for us and our suppliers to invest in quality systems, capacity, and staff. We have backup suppliers to create redundancy. And we maintain 6 months of safety stock.

Civica prefers to buy American where possible, then from other highly regulated economies, avoiding Chinese ingredients in all our drugs, if possible. Finally, Civica selects medicines to make based on the needs identified by pharmacists and physicians on the front lines.

To further support a resilient supply chain, Civica recently entered partnership with Flo and the Federal Government to make essential drugs here in the United States. This agreement will result in an end-to-end U.S. manufacturing supply chain for essential drugs which will be sold at Civica's nonprofit pricing.

As Congress considers other measures to improve the supply chain, we urge you to keep these principles in mind: define and focus on a set of essential drugs; support U.S. manufacturing; ensure redundant supplies and stockpiles; and purchase from companies with robust quality systems.

My written statement addresses specific policy tools, and I welcome your questions. Thank you.

[The prepared statement of Mr. VanTrieste appears in the appendix.]

The CHAIRMAN. Before I ask questions, I want to make a comment—not to you two people on this panel, but to my colleagues on this committee raising issues of whether or not this committee, with this hearing or anything else that has been done since the pandemic hit, whether or not we have been putting our attention in the proper direction. And obviously a lot of my Democrat colleagues feel otherwise.

So it appears that these number of Democrat colleagues who commented today—and maybe some who did not comment, because the usual courtesy that goes on in this committee was absent today—whether it is the colleagues who commented or not, they surely have been out of touch with what the committee has been doing recently, based on their comments.

I mentioned in a previous response to Senator Brown the billions of dollars this committee was involved in with responding to the COVID crisis and the economic turmoil that has resulted from it. And I guess some of my colleagues think that you just somehow pass a bill and then you forget about it. But our staffs, and at least some members, have spent weeks following up and assisting in implementing the $3-trillion relief package that we passed.

In addition, I have heard other complaints today. So I guess these colleagues on other issues are not aware that I have been working with Ranking Member Wyden to have an unemployment insurance hearing next week.

I also have sent oversight letters regarding the nursing homes that I am awaiting information on before any potential hearing, because you ought to have your ducks lined up before you take all the action that goes into a hearing, if you want that hearing to be productive.

So the bottom line is this: I request, before complaining in the future, it would be helpful to talk to me or have your staff talk to the staff of this committee. So in the end, then, if you did that, you would have a better idea of what we are talking about and what we have been doing, besides what is already on the public record, in regard to our response to the pandemic and our response to the economic turmoil caused by the shutting down of the economy by our government and our efforts now to bring it back up.

So I am going to start my questions with Mr. VanTrieste of Civica, who collaborated with HHS, Veterans Affairs, Department of Defense, CMS, and is working with the Trump administration Biomedical Advanced Research and Development Authority on a new manufacturing plant in the United States. What the purpose of the plant is, as I understand it, is to expand generic pharmaceutical manufacturing in the United States and create stockpiles of active pharmaceutical ingredients for public health agencies, which I guess in turn would make us less dependent on China and other countries.

So my first question is, has the Trump administration been a good partner in trying to overcome the issues of generics in short supply?

Mr. VANTRIESTE. I started my testimony today by acknowledging the hard work and dedication of many public servants who are working to protect the American people. Even before the pandemic hit, we had been talking with officials at BARDA, ASPR, and HHS who were focused on securing the pharmaceutical supply chain who have been interested and very helpful.

Because we have a direct relationship with pharmacists and physicians on the front lines of the pandemic, we have been able to provide information that helped inform their priorities concerning what are the essential generic medications during COVID.

I have to also add that since COVID, my faith in public servants has only gone up. These individuals have worked 24/7 around the clock to make sure that they can do the best job possible to bring good PPE, medical devices, testing, and drugs to those in the American public who need them the most.

The CHAIRMAN. My last question to you would be this: based upon your experience working with various government agencies,

how could Congress assist in strengthening and promoting U.S. drug manufacturing companies to return to the United States?

Mr. VANTRIESTE. So I think clearly—I hear frequently of organizations or individuals interested in starting their own nonprofit pharmaceutical company. Some are interested in the trouble with drug shortages; others in reducing drug prices; and still others are looking to solve a market failure, such as a need for new antibiotics or therapies for neglected diseases in which the traditional commercial model is not working.

Nonprofit pharma has a great potential, not as an alternative to for-profit industry but as an adjunct for or a complement to it. But there are several things that would help this emerging model succeed. We should recognize that nonprofits cannot raise capital the same way that the private sector does. Civica benefits from the financial commitments of our health systems and philanthropies, but in some cases the government itself may want to look at the model as a solution to the problem.

Using grants, low-interest loans, or other public/private mechanisms would help the nonprofit pharma industry blossom. But in addition, there are a great number of bills that have been introduced in Congress recently, some very bipartisan like with Senator Warner and Senator Rubio, that talk about incentives to re-shore the American pharmaceutical industry and bolster the supply chain. Civica has publicly said that they acknowledge and applaud those efforts.

The CHAIRMAN. I thank you very much, and my last two or three questions will be to Mr. Light. So I will ask you, do I understand that your business model includes testing drugs before dispensing them to patients? Would you provide the committee a couple of examples of toxins and other impurities your testing process has detected in drugs to make them safer and more effective?

Mr. LIGHT. So we test, actually, for a whole variety of components in drugs, including dosage; the inactive ingredients; the dissolution rate, which is how a pill dissolves in one's stomach or intestines; and a variety of carcinogens, such as NDMA, which has been discussed extensively.

I will say that everything that we have looked for, we have found problems with, some more than others, and I think there has been a lot of attention—rightly so—to the carcinogens. Just last week there have been recalls on a new drug, metformin, due to the same carcinogen, NDMA. And we test for a variety of these on all the batches through our pharmacy.

The CHAIRMAN. My second question would be about your relationship with FDA. When you discover contaminated drugs, do you report it to the FDA? And if so, what has been the FDA's response?

Mr. LIGHT. Because we are actually outside of the manufacturing system, we are not a good manufacturing facility because we do not manufacture. We are a pharmacy that has a laboratory. And so the guidance we receive from the FDA is to report these findings to industry, which has the freedom not to pay close attention to them, given that we are not a GMP facility.

I think it really underscores the point that independent analyses, certainly a lot from academics, have been largely ignored because we are not part of this pharmaceutical regulatory bubble. However,

we have effectively utilized the mechanism FDA has of an FDA citizen petition where, when we have sufficient data in-depth on particular problems like Zantac or metformin, we file a petition with this data and ask for actions of the FDA, such as to make these recalls.

The CHAIRMAN. Can you describe the process you use to test those drugs, and how much does the process cost?

Mr. LIGHT. The process we use will certainly depend on the particular analysis. We have some amount of proprietary technology that we also use industry-standard technologies with. We have optimized these systems so that we add less than a penny per pill of cost generally, and we sell these medications at no additional cost to patients. So this cost of independent analysis adds very little to the actual pill cost of being able to dispense it to a patient at the pharmacy level, and we believe that at larger levels, potentially even doing this with manufacturers, there is a very small additional cost.

The CHAIRMAN. My last question to you: how do you see your system impacting drug manufacturing?

Mr. LIGHT. We certainly hope to improve the system as a whole. I think we have already seen the proof of principle in key drugs like metformin and Zantac, and we certainly hope that quality manufacturers will see this as an opportunity, which has been discussed a few times during this hearing, of rewarding quality manufacturers, whether that is through advanced quality management maturity or, from our perspective, a science- and evidence-based approach where we can actually infuse this independent analysis in addition to what the manufacturers already do, and make that transparent to patients, buyers, and payers throughout the United States.

The CHAIRMAN. Before I close, I want to thank the two witnesses right now who are still here. But I was away voting on the Senate floor when the first panel left. I did not get a chance to thank them, as chairman of this committee. I want to do that.

So, whether you are government or private-sector witnesses, we appreciate your attendance today. COVID has created many logistical hurdles in making today's hearing—oh, did I forget Senator Wyden?

Senator WYDEN. Yes, Mr. Chairman, I have a couple of additional questions.

The CHAIRMAN. I really apologize. I am sorry. I will leave my closing statement to when you get done.

Senator WYDEN. Okay. I just have a couple of questions here for the gentleman from Civica, Mr. VanTrieste, if I am pronouncing that right. And then I want to make a comment to see if we can take some constructive measures going forward.

Let me just make sure we have got this. Mr. VanTrieste, your company is part of a contract that the Trump administration recently awarded to make COVID–19 drugs. Which drugs are you manufacturing right now?

Mr. VANTRIESTE. So the intent of the grant that was given to us by BARDA was not to be making drugs or APIs, it was to put the infrastructure in place for the next pandemic, or the next crisis.

However, Civica already had a series of drugs that we provide our members for use during a pandemic, and those include antibiotics, cross-spectrum antibiotics, sedation agents, heart medications, and local anaesthetics. We have sent over 1.6 million vials at the request of the government to the strategic national stockpile, and we are prepared to provide more if asked.

Senator WYDEN. So I just want to make sure we are clear. You got this contract, and you said something about working on infrastructure for the future—always useful—but I am not clear what you are doing with this contract as it relates to COVID–19 drugs now. Have you given some COVID drugs to the government that we do not know about?

Mr. VANTRIESTE. Yes. We provided over 1.6 million vials of drugs to support COVID patients like cross-spectrum antibiotics, sedation agents, heart medications, and local anaesthetics. These are the same products that we provide our members on a routine basis. They include vancomycin, ketamine, lidocaine——

Senator WYDEN. You were doing that before the COVID–19 pandemic, were you not?

Mr. VANTRIESTE. We were not supplying the national stockpile.

Senator WYDEN. But you had the drugs?

Mr. VANTRIESTE. We had the drugs.

Senator WYDEN. Okay. I am just trying to find what value-added the government got for its money, and I would like to know what drugs is the prime contractor making?

Mr. VANTRIESTE. So the prime contractor is making an API facility that will produce active pharmaceutical ingredients and their precursors, which we are really dependent on China for, as people talked about earlier, especially the precursors. And this is using brand new technology called "advanced manufacturing," but it is not for today, it is for the future. And this contract has not been designed to set up manufacturing for today, but in the future, Senator.

Senator WYDEN. I appreciate that, and I am always interested in the future. But I am interested in the urgency of communities devastated by COVID–19 now and getting them help now, and I am still unclear how anything you are going to do with these new efforts addresses that. My time is short, and I am going to have to just make one last point that addresses what the chairman talked about.

Mr. Chairman? I am looking for where the chairman is. Is the chairman still——

The CHAIRMAN. Yes?

Senator WYDEN. Okay, there is the chairman, all right.

I want to just make a brief comment to my friend with respect to the afternoon. Because I have been here, like the chairman, for about 3½ hours, and I think that what my colleagues and I have raised is not a question primarily of courtesy—because I think all have been reasonable in tone—but it reflects an urgency.

The racial injustice, for example, in American health care is an immediate need. The African American community, as we have been talking about, has been hit by COVID–19 like a wrecking ball. And on our side of the aisle, we want to make sure the Finance Committee—which has such enormous power in health care over

Medicare and Medicaid and the exchanges, and literally $2 trillion annually—is going to use its extraordinary muscle in order to make sure the African American community that has been hit so hard, that is responding right now to injustices all across the country, is going to see us use our influence to get those communities of color a fair shake in American health care.

And so we had colleagues on our side raise this repeatedly, and unless I am missing something—because I could have been out for a minute—no one on the other side of the aisle raised it. I think that is unfortunate.

So to try to see if we could end on a positive note, Mr. Chairman, can we agree, you as the chair and I as the ranking minority member, that we will task our staffs and members on both sides to move very quickly to put together a hearing and an agenda, an actual specific action agenda, to use the muscle of our committee to deal with these racial injustices? You and I are the only ones left. We have been here for 3½ hours, and that is something that we can take from this in a positive way that, going forward, we will work together with our staff, with our colleagues, to put together a hearing quickly and an action agenda to deal with these racial injustices that so many African Americans are telling us about, literally for hours each day.

Is that something we can agree on?

The CHAIRMAN. We can always sit down and discuss anything you want to discuss, as you will sit down with me any time I suggest we discuss things. I guess the only thing I would ask you to take into consideration is, almost every program that we are involved in on this committee, whether it is Social Security going back to 1936, whether it is Medicare and Medicaid going back to 1966, or whether it is unemployment compensation that has been around I think since the 1930s, all of these programs are color-blind. You have to realize that. And we will continue to work in a color-blind way, because we are all Americans, and we have to pull together, and we should not leave anybody behind. And my goal is not to leave anybody behind.

Senator WYDEN. Mr. Chairman, just, if I might, I will tell you, respectfully, it is very clear that these health-care programs are not color-blind. We have seen study after study showing that communities of color are disproportionately affected by these health problems that we are talking about, and that services, for example, do not even come to their communities.

We have been hearing, as I have in the last few days, that in the health legislation, the affluent hospitals did incredibly well. And in communities of color, there were not very many hospitals, and those there did not have the services that folks need.

So I will leave this, and I hope that we can work this out quickly. And, respectfully, I will say again, Mr. Chairman, the facts show that these programs are not color-blind. The hard evidence shows the disproportionate effects on communities of color by these health programs. And for that reason, we would like to work as the Finance Committee has always done in a constructive way to get a hearing quickly to develop an action plan to reverse these injustices.

The CHAIRMAN. It is against the law for all these programs to discriminate against anybody.

I will close with this. Before we formally close today, I once again, for the second time, thank our witnesses, government and private-sector, for their attendance today.

COVID has created many logistical hurdles in making today's hearing happen. I appreciate all that people have done, for being a part of this very important discussion. In addition, I want to thank the clerk staff for their hard work, time, and attention in making this hearing happen.

Today we have discussed many important issues that have existed for decades. However, because of the pandemic they are now more important than ever before. Congress must ensure that the executive branch takes all the necessary steps to properly oversee the drug supply chain. We must work together to ensure safe and effective drugs. We have a good idea of who the bad actors are in the drug supply chain. We also know that aggressive and unannounced inspections provide the best way to catch those bad actors.

I fully expect HHS and its subcomponents to laser-focus on them aggressively, engaging in inspections as well as enforcement. Today we have highlighted one aspect of the drug supply chain: that supply chain ends in the United States. Going forward, we must entertain serious policy discussions about how we can efficiently and safely bring manufacturing back to the United States. In the coming weeks, I will be working on the next focus: the personal protective equipment supply chain.

With that, the hearing is over, and members have 1 week to provide questions for the record. And whether it is this panel or the previous panel, I hope you will respond appropriately and as quickly as you can.

Meeting adjourned.

[Whereupon, at 5:30 p.m., the hearing was concluded.]

APPENDIX

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

PREPARED STATEMENT OF MARK ABDOO, ASSOCIATE COMMISSIONER FOR GLOBAL POLICY AND STRATEGY; JUDITH MCMEEKIN, PHARM.D., ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS; AND DOUGLAS C. THROCKMORTON, M.D., DEPUTY DIRECTOR FOR REGULATORY PROGRAMS, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Chairman Grassley, Ranking Member Wyden, and members of the committee, thank you for the opportunity to testify today on a matter of the utmost importance to the agency: protecting the safety, quality, and availability of medicines for Americans.

The U.S. drug supply is among the safest in the world. FDA thoroughly reviews drug applications to ensure that medications are safe and effective before they reach the market and oversees drug quality post-approval. The agency inspects drug manufacturing facilities located around the world with comparable depth and rigor based on an assessment of risk to public health. FDA laboratories test for drug quality, using testing standards set by the United States Pharmacopeia, or standards submitted in marketing applications, or methods developed by FDA. This testing has consistently shown that medicines manufactured in foreign countries that are imported into the United States meet U.S. market quality standards. When FDA identifies significant manufacturing or safety issues, it quickly acts to protect Americans.

During the COVID–19 pandemic, FDA is continuing to utilize and implement additional alternative inspection tools and approaches while postponing foreign and domestic routine surveillance facility inspections. This will continue as conditions warrant, with the exception of certain mission critical inspections, including pre-approval and for-cause assignments. Mission critical inspections are identified on a case-by-case basis and conducted with appropriate safety measures in place.

Importantly, during this interim period we're evaluating additional ways to conduct our inspectional work that would not jeopardize public safety and protect both the firms and the FDA staff. This can include, among other things, evaluating records in advance of or in lieu of conducting an onsite inspection when travel is not permissible, when appropriate. We want to assure the American public that we have full confidence in the safety and quality of the products we all use every day and that the FDA will continue to leverage all available authorities to continue to ensure the integrity of the products we regulate.

Today we will provide the committee with an overview of the history of FDA's foreign drug inspection program, and the ways it has evolved in response to the industry's globalization and changes in law and regulation. We will also explain our approach when our inspections indicate that a facility does not operate in keeping with established quality standards. These standards are known as current good manufacturing practices (CGMPs). We will also describe some potential enhancements that would enable FDA to complement our foreign drug inspection program. The agency believes that over the longer term, we should encourage investment in advanced manufacturing technology and in strengthening the approach by which manufacturers assure the quality of their products. This approach, which we call quality management maturity, would provide a safer and more secure drug supply because it can help prevent many quality problems from occurring in the first place. Advanced technology, which can be more cost-effective and environmentally friendly than tra-

ditional manufacturing technology, may also enable the United States to play a larger role in pharmaceutical manufacturing.

THE GLOBALIZATION OF PHARMACEUTICAL MANUFACTURING

Over the past 30 years, pharmaceutical manufacturing has become an increasingly global enterprise. Beginning in the 1970s, industry moved away from the mainland U.S., first to Puerto Rico in response to tax incentives, and then to Europe and nations that were developing at the time, such as China and India. Developing nations can provide significant cost savings to pharmaceutical companies because of their lower labor, energy, and transportation costs. In addition, they often have weaker environmental regulations than more developed countries. A World Bank study estimated that in 2004, China and India held a cost advantage of about 40 percent when compared with the U.S. and Europe.[1] FDA's 2011 report, "Pathway to Global Product Safety and Quality," also noted that both China and India enjoy a labor cost advantage and that manufacturing active pharmaceutical ingredients (APIs) in India can reduce costs for U.S. and European companies by an estimated 30 percent to 40 percent.[2]

As the U.S. drug market shifted toward lower-priced generic drugs, manufacturers came under increasing cost pressure and found these efficiencies compelling reasons to locate more of their facilities overseas, particularly in developing parts of the world. This shift is reflected in the Center for Drug Evaluation and Research's (CDER's) Site Catalog ("Catalog"), which lists all drug manufacturing facilities worldwide that are subject to routine FDA inspections.[3] As of May 2020, 26 percent of facilities manufacturing APIs and 46 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the U.S. (See Figures 1 and 2)

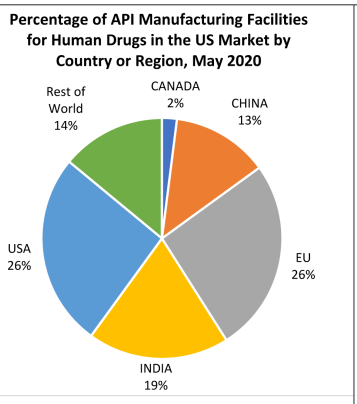

Figure 1: For all FDA-regulated drugs, 26 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

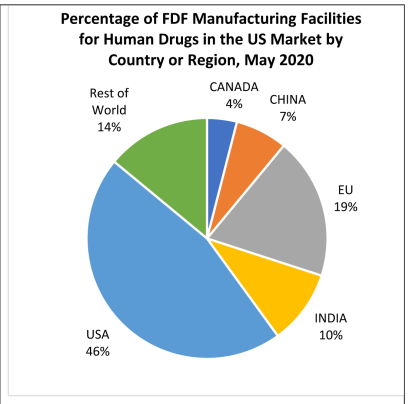

Figure 2: For all FDA-regulated drugs, 46 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

This movement accelerated in the 2000s, but due to statutory mandates for biennial domestic inspections and limited staffing, FDA's inspectorate remained focused on domestic manufacturing. Until passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 (Pub. L. 112–144), the agency was legally required to inspect manufacturing facilities in the U.S. every 2 years but had

[1] Bumpas, Janet; Betsch, Ekkehard. *Exploratory study on active pharmaceutical ingredient manufacturing for essential medicines (English).* Health, Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank: 12–13, Figure 2. *http://documents.worldbank.org/curated/en/848191468149087035/Exploratory-study-on-active-pharmaceutical-ingredient-manufacturing-for-essential-medicines*. Accessed September 30, 2019.

[2] U.S. Food and Drug Administration, "Pathway to Global Product Safety and Quality," A Special Report, p. 20. Accessed October 4, 2019 at *https://www.hsdl.org/?view&did=4123*.

[3] The agency updates the Catalog continually, so the information it provides is a snapshot in time.

no similar mandate for the inspection frequency of foreign facilities. This resulted in more frequent inspections for domestic facilities.

The Globalization of FDA's Drug Inspection Program

In response to the move from domestic to global manufacturing and the passage of FDASIA, FDA developed and implemented a comprehensive strategy to facilitate greater coordination and oversight of medical products. In addition to increasing foreign inspections, our efforts have included:

- Developing new enforcement and regulatory tools;
- Increasing collaboration with foreign regulators and other stakeholders;
- Developing internationally harmonized standards and standards convergence;
- Educating foreign industry about FDA requirements;
- Increasing transparency and accountability in the supply chain; and
- Establishing foreign offices with an overseas footprint in China, India, Europe, and Latin America.

Responsibility for addressing these global issues is distributed across the agency. The Office of Regulatory Affairs (ORA) conducts inspections and reviews imported products offered for entry into the United States. FDA's product centers focus on international policy and outreach that touches on their portfolio of regulated products. The Office of Global Policy and Strategy serves as a focal point for FDA-wide coordination and information-sharing and a point of access to multilateral organizations; addresses issues related to international trade of regulated products and mutual recognition agreements; enters into arrangements that facilitate the sharing of information with global regulatory counterparts; and manages FDA's foreign offices around the world.

FDA's drug inspection program shifted from one focused heavily on U.S.-based facilities through the early 2000s to a program that, since 2015, has conducted more foreign than domestic drug inspections. (See Figure 3) FDA's drug inspection program is now risk-based. FDA prioritizes for inspection facilities deemed higher-risk based on specific, defined criteria.

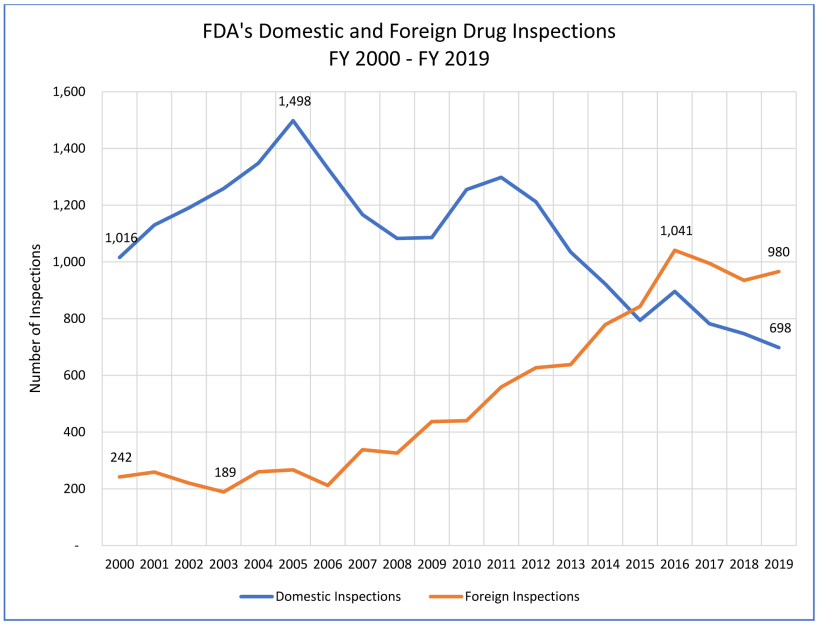

Figure 3: FDA's Inspections of Foreign Drug Manufacturing Facilities Increased Sharply After 2006 and Have Exceeded Inspections of Domestic Drug Facilities Since 2015

Types of Inspections

The types of inspections performed in both domestic and foreign facilities include *pre-approval, surveillance,* and *for-cause inspections.*

- *Pre-approval inspections:* conducted as part of the review of an application to market a new brand or generic drug.
- *Surveillance inspections:* Used to monitor the manufacturing process and the quality of distributed drugs. FDA uses the findings to evaluate whether a manufacturer is complying with CGMPs. In general, the agency does not announce domestic surveillance inspections to the company in advance but usually announces foreign surveillance inspections in advance, partly due to logistics such as arranging travel and access to facilities, securing visas, and partly because of the high costs of conducting foreign inspections. Whether inspections are announced often depends on particular cases and the history of specific facilities.
- *For-cause inspections:* Triggered when FDA has reason to believe that a facility has serious manufacturing quality problems or when FDA wants to evaluate corrections that have been made to address previous violations. For-cause inspections can be announced or unannounced, whether domestic or international, depending on the specific situation.

When the agency has determined the need to do an unannounced inspection, FDA has conducted such operations. Over the past several years, FDA investigators have conducted unannounced inspections at foreign manufacturing facilities, including in India and China. When significant issues are uncovered at a foreign manufacturing facility, the agency uses additional tools to protect patients including placing the facility on import alert, which is used to prevent potentially violative products from entering the U.S. market.

THE SITE SELECTION MODEL

To address the need to prioritize use of limited resources, in 2005 FDA implemented a risk-based approach to drug facility surveillance inspections. A mathematical model, the Site Selection Model (SSM), was designed to select facilities with the greatest potential for public health risk should they not comply with established manufacturing quality standards. FDA uses results of the model to prepare a prioritized list of facilities for inspection.

The passage of FDASIA ratified our risk-based approach and removed the requirement to inspect domestic facilities on a fixed biennial schedule. FDASIA also enhanced our inspectional authority by requiring facilities to provide, upon request, records or other information in lieu of or in advance of an inspection. Additionally, under another provision added by FDASIA, if the owner or operator of a foreign facility delays, denies, or refuses to permit inspection, all drugs manufactured at that facility would be deemed "adulterated."[4] The agency thanks Congress for enacting this law.

In 2007, FDA began planning the shift of its investigator workforce to cover foreign facilities and to balance allocation between domestic and foreign inspections. Both the Generic Drug User Fee Amendments (GDUFA) of 2012 and its reauthorization in 2017 provided new resources to FDA for inspecting foreign facilities, which as we have noted are often the source for APIs and FDFs of generic drugs.

With new resources, FDA has been able to inspect some facilities that previously had not been inspected. Catalog showed that as of December 2016, there were 963 foreign manufacturing facilities that had never been inspected by FDA. All of the 963[5] foreign manufacturing facilities that GAO reported to be uninspected (as of December 2016) have now been addressed. By the end of FY 2019, FDA had inspected 496, or approximately 52 percent, of these previously uninspected facilities. (See Figure 4) An additional 361 facilities (37 percent) were removed from the Catalog because they were no longer part of FDA's inspection obligations for a number

[4] The Federal Food, Drug, and Cosmetic Act (FD&C Act) describes different circumstances in which a drug may be considered adulterated. For example, a drug might be adulterated where it is contaminated with filth, where its purity departs from certain compendial standards, or where the conditions of its manufacturing are not consistent with current good manufacturing practice (CGMP).

[5] The 2016 GAO report identifies 965 firms that, at that time, had not been inspected. Since then, there were two separate mergers of facilities in that count, dropping the number from 965 to 963.

of reasons, *e.g.,* they had gone out of business, were not serving the U.S. market, or had been registered with FDA erroneously. In addition, 52, or 5 percent, of the facilities had refused inspection;[6] 34, or 4 percent, of the facilities were inaccessible to FDA investigators because they were unable to travel to them (*e.g.,* as a result of travel warnings); and 20, or 2 percent, had no imported drug shipments to the U.S.

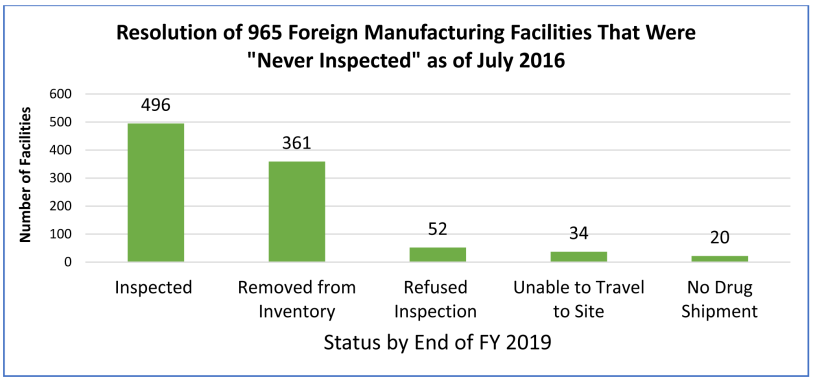

Figure 4. FDA has now evaluated all previously "never inspected" facilities

The SSM is at the core of FDA's surveillance inspection prioritization program and ensures a uniform approach for domestic and foreign facility inspections. The agency uses the model to calculate a score for every facility in its Catalog using risk-based factors. Factors in the SSM include:

- **Inherent product risk.** Different types of products carry different levels of risk based on characteristics such as dosage form, route of administration, or whether the product is intended to be sterile. For example, a manufacturing facility that makes sterile injectable drug products will have a higher inherent product risk than a facility that makes oral capsules.
- **Facility type.** Risk levels can vary depending on the operations that a facility performs. A facility that manufactures drug product or active ingredients is higher in risk than a facility that only packages drug product.
- **Patient exposure.** The more products a facility manufactures, the more likely a patient is to encounter products made at that facility. This refers to both number and types of products manufactured. A facility that manufactures many products will have a higher exposure factor than a facility that makes few products.
- **Inspection history.** A facility that has not met established quality standards when previously inspected is considered higher risk than those that have met standards in the past.
- **Time since last inspection.** As the time since a facility was last inspected increases, the risk that it may not meet established quality standards increases, as does the need for re-inspection.
- **Hazard signals.** Events such as product recalls or manufacturers' or patients' reports of quality problems associated with a facility increase the risk score when compared with facilities that have fewer or no major hazard signals.

FDA compares a facility's score to others in the Catalog and ranks them by risk, with the highest risk assigned for inspection regardless of location.

If the three factors that are fairly static for a facility (inherent product risk, facility type and patient exposure) are used to risk rank facilities, for inspections con-

[6] Under the FD&C Act, as amended by FDASIA, a drug product will be deemed adulterated if it has been manufactured, processed, packed, or held in any factory, warehouse, or establishment which delays, denies, or limits an inspection, or refuses to permit entry or inspection. In such a case, FDA typically will place the firm on import alert.

ducted from December 2011 to May 2020, the median time between inspections was 2.1 years for high-risk facilities. In general, all high-risk facilities were inspected with about the same frequency regardless of location. (See Figure 5)

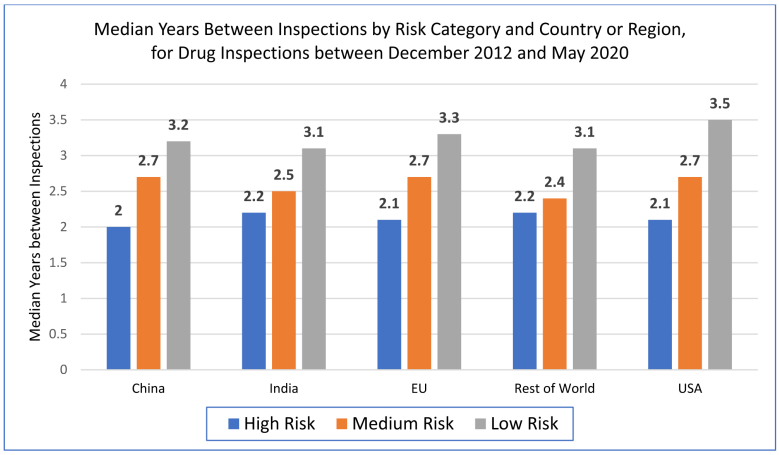

Figure 5. FDA inspected high-risk manufacturing facilities more frequently than medium- or low-risk facilities, and medium-risk facilities more frequently than low-risk facilities, across all countries or regions. In general, all facilities in a risk category were inspected with about the same frequency, regardless of location.

Inspection Outcomes

Following inspection of a manufacturing facility, FDA classifies the inspection as "no action indicated" (NAI), "voluntary action indicated" (VAI), or "official action indicated" (OAI).

- *No Action Indicated (NAI)* means that no objectionable conditions or practices (*e.g.,* quality problems) were found during the inspection (or they were minor problems that do not justify further regulatory action).
- *Voluntary Action Indicated (VAI)* means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action.
- *Official Action Indicated (OAI)* means regulatory and/or administrative actions will be recommended.[7]

Not surprisingly, with more frequent inspections directed to higher-risk facilities since 2012, FDA uncovered more deficiencies, particularly in foreign facilities that had not been inspected as frequently as domestic ones prior to the inception of FDASIA and GDUFA. Notably these were foreign inspections that were generally announced to facilities in advance (pre-announced). Nevertheless, 90 percent or more of the final outcomes of inspections were acceptable (NAI or VAI) in all countries or regions except India. (See Figure 6)

[7] See "What Is a Classification?" at *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions.*

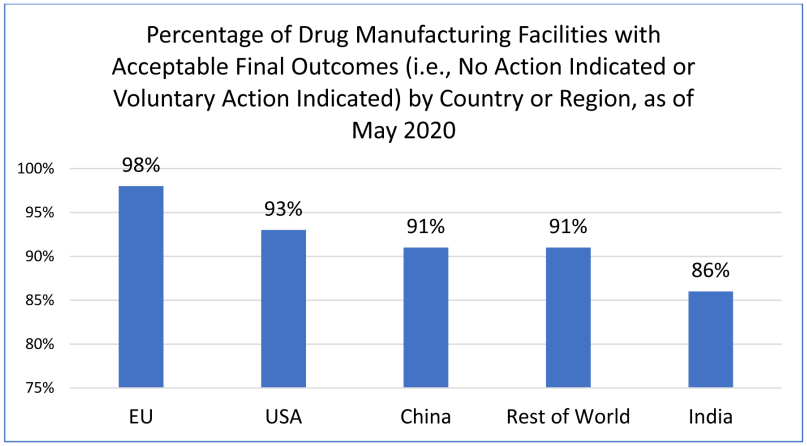

Figure 6. The majority of final inspection outcomes for manufacturing facilities making human drugs were acceptable, meaning that they were classified as having No Action Indicated or Voluntary Action Indicated. However, India had a lower percentage of acceptable outcomes than other countries and regions. (These were outcomes as of May 2020 for the most recent inspection of facilities within FDA's Catalog.)

Both foreign and domestic drug manufacturers must meet the same regulatory requirements in terms of complying with established quality standards (CGMPs). If a facility doesn't meet CGMP standards upon inspection, FDA has an array of regulatory tools it can use to encourage a company to remediate their manufacturing processes and achieve compliance. These tools include warning letters, import alerts, injunctions, and seizures.[8] If the agency observes on a follow-up inspection that a facility still does not meet CGMP standards, it can escalate the matter as appropriate.

If a foreign facility is found to have quality problems serious enough for FDA to classify it as OAI, the agency can place a facility on Import Alert, which is used to prevent potentially violative drugs from the facility from entering the U.S. Generally, FDA will remove a facility from a CGMP-related Import Alert after an onsite re-inspection demonstrates that the problems have been remediated and the firm is in compliance with CGMP.

Despite the tools at FDA's disposal, we still face some challenges in ensuring the safety of imported drugs entering our drug supply. Current mandates for facility inspection prior to import or marketing of a drug in the U.S. are typically in the context of premarket approval requirements. For drugs that are subject to premarket approval requirements, FDA has an opportunity to evaluate and inspect the manufacturing facilities as part of the application review process. However, for drugs that are not subject to premarket approval requirements, manufacturers may not be subject to FDA inspection before such products are shipped to or distributed in the U.S. Drugs in this category typically include OTC monograph drugs and APIs used in pharmacy compounding. FDA may be required to engage in more challenging and resource intensive efforts to identify and respond to any problems that arise subsequently; however, patients may have already been exposed to the drugs. For example, in 2019 we issued a warning letter to a discount retailer for receiving OTC drugs produced by foreign manufacturers with serious violations of CGMPs. The

[8] Import Alert: Import alerts inform the FDA's field staff and the public that the agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of the FDA's laws and regulations. These violations could be related to the product, manufacturer, shipper and/or other information.

majority of the foreign facilities involved had distributed drugs to the U.S. prior to FDA inspections.[9]

FDA's Program Alignment Initiative and Concept of Operations Agreement

The inspection of drug manufacturing facilities relies on the collaboration of two organizations within FDA: ORA, which includes the field force of investigators who conduct the inspections, and CDER, which includes policy and regulatory experts who establish the policies governing drug quality, assess risks, and review action recommendations, including OAI recommendations from ORA and for-cause inspections to determine the final classification and whether appropriate regulatory action is required. CDER also includes assessors who evaluate applications for marketing approval and post-marketing changes. In May 2017, as part of a broader agency initiative called Program Alignment, ORA implemented a program-based management structure aligning staff by FDA-regulated product. This created a specialized inspectorate focused on human drugs.

FDA modeled its oversight of the increasingly complex and global drug manufacturing supply chain to better integrate facility evaluations and inspections for human drugs—to improve our efficiency, reach, and the public health. In June 2017, CDER and ORA entered into a Concept of Operations[10] (ConOps) agreement to more effectively manage the growing complexity of the pharmaceutical landscape. The agreement, Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations, outlines the responsibilities and the workflow for pre-approval, surveillance, and for-cause inspections at domestic and international facilities.

As part of ConOps the decision classification workflow process was redesigned. (See Figure 7) Under the ConOps agreement, when ORA initially recommends classifying the inspection as OAI, CDER reviews the report along with any remediation plan or response submitted by the company. CDER evaluates the evidence supporting inspection observations, potential impact to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. CDER may reclassify the inspection based on this review. CDER also can, and has, upgraded classifications to OAI, even when initial recommendations from the field are for an acceptable classification. This typically occurs with for-cause inspections where the proposed corrective actions by the firm are determined by CDER to be inadequate.

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[9] *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/greenbrier-international-inc-dba-dollar-tree-574706-11062019.*

[10] See *https://www.fda.gov/media/107225/download.*

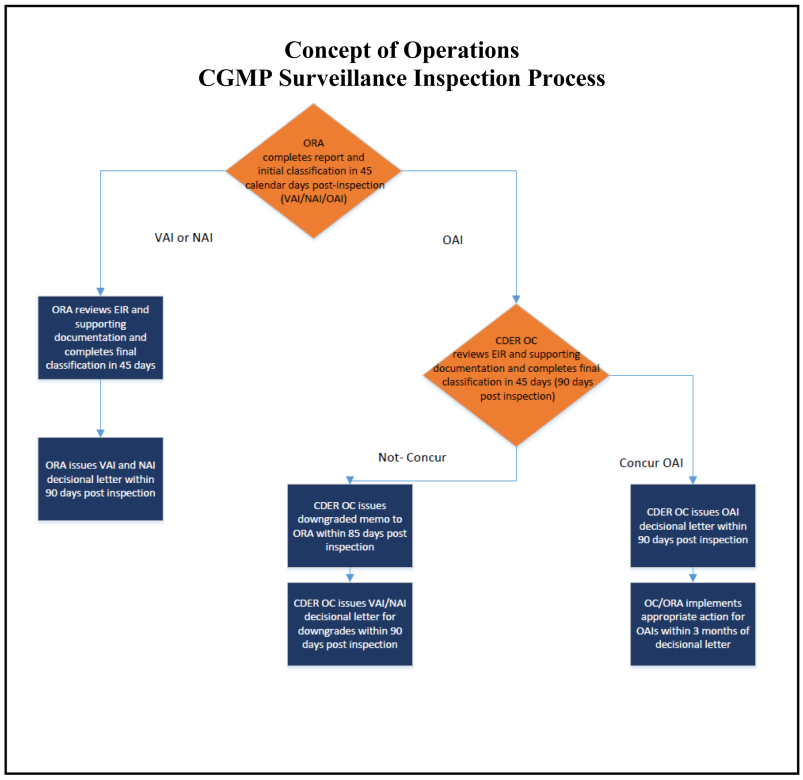

Figure 7. Process for classifying surveillance inspection outcomes after implementation of the ConOps.

Implementation of the ConOps has improved consistency in evaluation of inspection observations and classifications and has reduced the time frames for taking enforcement action. The percentage of cases in which CDER concurs with ORA's initial recommendation is known as the "concurrence rate." (See Figure 8) In 2019, the concurrence rate had risen to 73 percent.

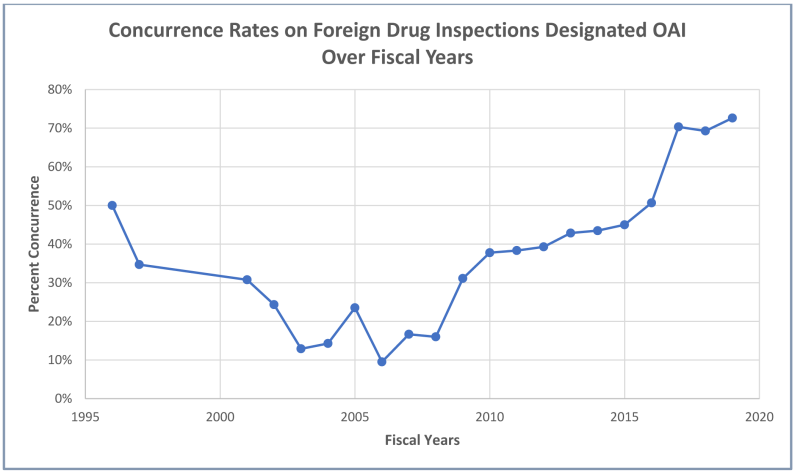

Figure 8. Concurrence rates on foreign drug inspections designated OAI were 50% in 1996 and rose to 73% in 2019. (FY 1996-1997 based on GAO data, all other data from FDA compliance database.)

The median time for FDA to issue a warning letter for drug manufacturing issues has decreased since ConOps was implemented, even though the number of warning letters FDA has issued has increased during that same time period. (See Figure 9)

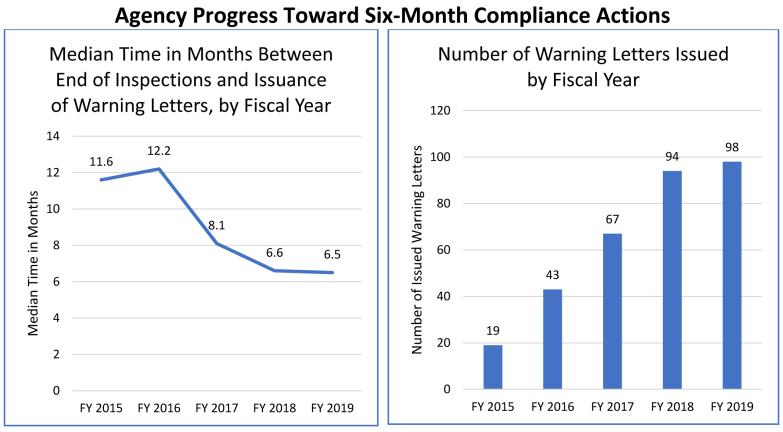

Figure 9. From FY 2015 to FY 2019 there has been an overall median 44% improvement in median time between the end of an inspection and issuance of a warning letter. During the same time, the number of warning letters increased.

Building an Investigator Work Force

Since 2015, FDA has performed more foreign than domestic inspections. The agency has done so by using a mixed investigator work force consisting of (1) U.S.-based investigators who perform both domestic and foreign inspections; (2) a dedicated foreign cadre of U.S.-based drug investigators who conduct foreign inspections exclusively; and (3) foreign office-based experienced investigators who inspect facilities manufacturing human drugs. (See Table 1) The majority of foreign inspections are performed by U.S.-based investigators.

Table 1. FDA's Investigator Work Force for Inspections of Foreign Facilities Producing Human Drugs, FY 2019

Type of Investigator	Number of Qualified Foreign Drug Investigators in FY 2019	Number of Foreign Inspections Each Investigator is Expected to Perform Each Year	Estimated Percentage of All Foreign Inspections Performed in FY 2019
U.S.-Based Investigators Performing Foreign and Domestic Inspections	188	3–6 foreign inspections per year	90%
Dedicated Foreign Drug Cadre Based in U.S.	11 (included in the 188 listed above)	16–18 inspections per year	16% (part of the 90% above)
Foreign Office-Based Investigators	10	15 inspections per year	10%

During calendar year 2019 ORA successfully hired and on-boarded 24 pharmaceutical investigators. In 2020 our investigator hiring efforts are continuing, and with our new direct hire authority we anticipate filling all our pharmaceutical investigator vacancies in 2020. In recent years, the Office of Global Policy and Strategy, which oversees FDA's foreign offices, has made progress in developing the foreign office-based inspectorate. At the same time, FDA's participation in the Mutual Recognition Agreement with the European Union has enabled us to focus more of our investigator work force on higher-risk facilities around the world.

The agency continues to face challenges, however, in developing the investigator work force due to the rigorous nature of the job (*e.g.,* foreign travel restrictions and hardship) and competition for qualified candidates. Once the agency succeeds in hiring a new investigator, it can take 1.5 to 2 years of training to bring them to a fully proficient level. FDA also faces challenges to achieving optimum staffing levels, such as negotiated agreements with host countries that affect the number of investigators who can permanently attach to a foreign office.

COVID–19 and Inspection Impact

As noted at the beginning of this testimony, as a result of the COVID–19 pandemic, most foreign and domestic surveillance facility inspections are currently postponed. Only inspections deemed mission-critical will be considered on a case-by-case basis as this outbreak continues to unfold.

We employ additional tools to ensure the safety of products imported to the U.S., which have proved effective in the past. These include:

- Denying entry of unsafe products into the U.S.;
- Physical examinations and/or product sampling at our borders;
- Reviewing a firm's previous compliance history;
- Using information sharing from foreign governments as part of mutual recognition and confidentiality agreements; and
- Requesting records "in advance of or in lieu of" on-site drug inspections.

Through our risk-based import screening tool (PREDICT), FDA has the ability to focus our examinations and sample collections based on heightened concerns of specific products being entered into U.S. commerce. The PREDICT screening continues to adjust risk scores as necessary throughout the COVID–19 outbreak.

FDA investigators remain on the front lines at ports of entry, quickly examining and reviewing import entries to help ensure goods being imported are consistent with FDA requirements and/or policies. We are in close communication with our partners at U.S. Customs and Border Protection to proactively identify and mitigate any potential backlogs.

FDA participates in FEMA Supply Chain Task Force meetings, providing regulatory support and subject matter expertise to respond to questions concerning medical products identified by FEMA, to facilitate the lawful entry and use of imported medical products coordinated through FEMA, and to inform medical product supply chain discussions.

FDA remains committed to using all available tools to oversee the safety and quality of FDA-regulated products for American patients and consumers. As this remains a dynamic situation, we will continue to assess and calibrate our approach as needed and we stand ready to resume any postponed inspections as soon as feasible.

FDA's Sampling and Testing Program

Although application assessments and inspections are a foundation of FDA's efforts to maintain a safe, reliable drug supply, the safety and effectiveness of drugs depends on a multipronged approach, of which quality checks by FDA and manufacturers are a part. To help ensure that safe and effective drugs are sold in the U.S., we test selected drugs in state-of-the-art FDA laboratories and through research contracts and grants. This testing program includes APIs and finished drug products. We test using the same standards that are part of the drug approval process for identity, strength, and purity.

Some have questioned why we do not test every drug product before it enters the U.S. FDA performs thousands of tests a year pre- and post-market. Only a small percentage (about one percent) of drugs that are tested fail to meet the established quality specifications.[11] Testing by FDA or third parties of each batch of drug product in U.S. commerce, which amounts to millions of batches and trillions of individual tablets, capsules, and other dosage forms, before they enter the U.S. market would not be feasible at a practical level (in 2018, there were almost 186 trillion tablets and capsules on the U.S. market[12]) and the current approach is effective and efficient.

Additional Drug Safety and Surveillance Efforts

Ongoing review and surveillance efforts can identify new safety concerns that require quick action. When they do, the agency makes every effort to investigate potential health risks and provide our recommendations to the public based on the best available science.

As an example, in April, FDA requested that manufacturers withdraw all prescription and over-the-counter (OTC) ranitidine drugs from the market immediately. This was the latest step in an ongoing investigation of a contaminant known as N-Nitrosodimethylamine (NDMA) in ranitidine medications (one commonly known brand name is Zantac). FDA began an investigation into potential NDMA contamination in drug products containing ranitidine when it first obtained information that there was a possibility of impurities in those products. NDMA is a probable human carcinogen (a substance that could cause cancer).

Last summer, the agency became aware of independent laboratory testing that found NDMA in ranitidine. Low levels of NDMA are commonly ingested in the diet; for example, NDMA is present in foods and in water. These low levels would not be expected to lead to an increase in the risk of cancer. However, sustained higher levels of exposure may increase the risk of cancer in humans. The agency conducted thorough laboratory tests and found NDMA in ranitidine at low levels. At the time, the agency did not have enough scientific evidence to recommend whether individuals should continue or stop taking ranitidine medicines. FDA continued its investigation and warned the public last fall of the potential risks and to consider alternative OTC and prescription treatments.

New FDA testing and evaluation confirmed that NDMA levels increase in ranitidine even under normal storage conditions, and NDMA has been found to increase significantly in samples stored at higher temperatures, including temperatures the product may be exposed to during distribution and handling by consumers. The testing also showed that the older a ranitidine batch is, or the longer the length of time since it was manufactured, the greater the level of NDMA, possibly resulting in ranitidine product being above the acceptable daily intake limit.

Based on this information, FDA took swift action to assure that ranitidine products will no longer be available for new or existing prescriptions or OTC use in the U.S.

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[11] These are established in approved applications, and for many drugs also by USP *(https://qualitymatters.usp.org/what-usp-standard).*

[12] IQVIA. National Sales Perspective. 2014–2018. Extracted: August 2019.

FDA Encourages Industry to Invest in Mature Quality Management Systems and Advanced Manufacturing Technology

FDA inspects manufacturing facilities and takes action, if needed, to enforce CGMP quality standards and applicable regulations. The agency's investigators look for deficiencies in meeting CGMP standards, but these assessments do not measure how far the facility is above the minimum CGMP. Simple adherence to CGMP standards does not indicate that a firm is investing in improvements or planning or deploying advanced quality control techniques that could better enable it to prevent quality problems leading to supply disruptions.

This is why it is critical that industry evolve from meeting the minimum manufacturing quality threshold to achieving quality management maturity. Some pharmaceutical firms have been slow to implement robust, mature quality systems and the accompanying quantitative measures of quality that have been the foundation of success in other industries, such as automotive and aerospace.[13] These industries exercise quality oversight by continuously monitoring quality in real time during manufacturing of their products, and promptly correcting operations when needed. Numerous organizations and quality experts have worked to develop conceptual models and standards for advancing the maturity of industrial quality management systems. These models could be used more broadly in the pharmaceutical industry to improve the quality and reliability of the drug supply.

Many pharmaceutical manufacturers, whether domestic or foreign, have been slow to invest in these mature quality management systems because the market currently has no visibility into manufacturing facilities' quality. This lack of transparency reinforces competition based solely on price and disincentivizes companies from making investments in upgrading their facilities and quality practices until problems become frequent and severe enough to result in supply disruptions and drug shortages. As we have stated in our recent report, "Drug Shortages: Root Causes and Potential Solutions,"[14] a way to create incentives for manufacturers to invest in product quality is to develop and implement a rating system for quality management maturity that is based on objective criteria. Such a rating system could enable purchasers to compare differences in quality and choose whether to reward more reliable manufacturers financially and with increased market share.

In addition to quality management maturity, the agency encourages pharmaceutical manufacturers to invest in advanced manufacturing technology to improve their products and processes. Although widely used in some other industries, such as automotive, aerospace, and semiconductors, advanced manufacturing is now just beginning to be used by pharmaceutical companies. New technologies include "continuous manufacturing" (CM), wherein the finished drug product or active pharmaceutical ingredient is produced as a continuous stream, as opposed to traditional batch manufacturing where breaks or stops exist between different processing steps. In some examples of advanced pharmaceutical manufacturing, production can be continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage forms. Product quality can be precisely controlled with modern automation and control systems and can be closely monitored during production by using highly sensitive analytical tools. Other examples of advanced manufacturing include 3D printing, isolator technology, miniaturization, and robotics.

CONCLUSION

Thank you for the opportunity to discuss FDA's oversight of pharmaceutical manufacturing. COVID–19 has provided yet more proof that to protect the reliability and availability of drugs to treat Americans is of vital importance. We look forward to working with the committee and others to strengthen investment in modern manufacturing technology, establish incentives for mature quality management systems, and consider additional measures.

We are happy to answer any questions.

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[13] Fuhr, Ted, et al., 2015, *Flawless—From Measuring Failure to Building Quality Robustness in Pharma,* McKinsey and Company.

[14] *https://www.fda.gov/drugs/drug-shortages/agency-drug-shortages-task-force.*

QUESTIONS SUBMITTED FOR THE RECORD TO MARK ABDOO; JUDITH MCMEEKIN, PHARM.D.; AND DOUGLAS C. THROCKMORTON, M.D.

QUESTIONS SUBMITTED BY HON. CHUCK GRASSLEY

ANNOUNCED VERSUS UNANNOUNCED INSPECTIONS

Question. The Government Accountability Office has noted that almost all domestic inspections are unannounced; however, the FDA often pre-announces foreign inspections. In some cases, the FDA has provided 12 weeks of notice before a foreign inspection.

By providing advanced warning that an inspection will take place, doesn't it give bad actors time to hide the true nature of problems at their facilities? If not, why not?

Wouldn't unannounced inspections provide a more accurate view of whether or not foreign manufacturers are complying with quality control standards? If not, why not?

Answer. There are many critical variables that are weighed and assessed to determine whether an announced or an unannounced inspection approach will lead to the best inspectional information.

Unannounced inspections can facilitate the detection of facility violative conditions when firms are intentionally seeking to deceive the agency by falsifying records or by hiding violations in advance of an inspection. However, FDA investigators are trained to review records and to uncover data integrity issues and fraudulent data with techniques such as searching data audit trails. Therefore, both the hiding of reportable deviations and violations, and falsification of records may be uncovered. When the agency receives complaints, reports from confidential informants, or other information that suggests that serious violations are occurring, unannounced inspections may be used.

In many cases there are benefits to announced inspections and these include fostering a culture of cooperative continuous improvement for many establishments. Prior notice of an upcoming inspection ensures the correct subject matter experts will be available for an efficient, productive inspection and that appropriate firm representatives with the right expertise are available during the inspection.

Furthermore, unannounced inspections become impractical when conducting most foreign inspections. Foreign inspections require weeks of planning, with additional costs and administrative requirements, such as special visas and country permissions. Foreign travel to many countries can be difficult due to distance and means of travel, often involving many flights, plus train or car travel with one-way travel times encompassing entire days. This time and resource investment may be wasteful and unproductive if, upon arrival at the facility, FDA determines that the firm has ceased manufacturing the product of interest, or the firm is not operational (*e.g.,* shut down for cleaning), the facility has closed, or key manufacturer representatives are not available to participate in the inspection and therefore unavailable to respond to investigator questions. This expenditure of resources, when unproductive, is a lost resource that would have potentially been utilized as capacity to conduct other inspections (indirect cost of lost productivity). It is also important to note that foreign inspections require visa applications and other notifications of foreign governments as noted above. This leads to a possibility that manufacturers may become aware through informal channels of an upcoming unannounced inspection, eliminating the potential benefits of unannounced inspections.

We strategically continue unannounced inspection on a for-cause basis even in the foreign arena. FDA's in-country investigators who are attached to FDA's foreign offices conduct unannounced FDA inspections, but those resources are limited due to the challenges of recruiting and retaining experienced FDA investigators in these positions.

FDA will continue to actively evaluate establishing criteria to assess unannounced inspections in the foreign arena and how those can be practically incorporated into operations, balancing the requirements necessary to carry out inspectional assignments successfully while being good stewards of U.S. government resources to achieve the intended public health outcomes.

Question. When an inspection identifies manufacturing quality problems, what does the FDA do to inform entities along the supply chain that manufacturing problems have been found?

Answer. Drug product manufacturers have existing requirements to evaluate the quality of components before use in drug product manufacturing and conduct investigations and associated follow-up, as appropriate.

When quality problems are identified, FDA may issue warning letters to multiple responsible stakeholders within a supply chain. FDA also posts warning letters on its website and may also add the firm and product to import alerts, which are available to the public and industry to inform their compliance decisions. In some instances, FDA also maintains an Inspection Classifications Database,[1] which shows inspections conducted by FDA and assessments of regulated facilities. It can be used by entities along the supply chain to identify firms with a final inspection classification indicating whether the firm is in compliance with applicable laws and regulations.

Seizure and injunction are other possible actions that may be considered.

CDER RECLASSIFICATIONS

Question. This committee has talked with individuals associated with FDA's inspection and reporting process and CDER's review of those inspections reports. Some have told us that CDER tends to downgrade, or reclassify, inspections reports from "Official Action Indicated" to "Voluntary Action Indicated."

Why does CDER have a tendency, according to information provided to this committee, to reclassify inspection reports?

Answer. In June 2017, CDER and ORA entered into a Concept of Operations (ConOps) agreement to more effectively manage the growing complexity of the pharmaceutical landscape. As part of ConOps, the decision classification workflow process for inspections was redesigned. Under the ConOps agreement, when ORA initially recommends classifying an inspection as Official Action Indicated (OAI), CDER reviews the report along with any remediation plan or response submitted by the company. CDER evaluates the evidence supporting inspection observations, potential impact to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. CDER may reclassify the inspection based on this review. CDER also can, and has, upgraded classifications to OAI, even when initial recommendations from the field are for an acceptable classification. This typically occurs with for-cause inspections where the proposed corrective actions by the firm are determined by CDER to be inadequate.

Implementation of the ConOps has improved consistency in evaluation of inspection observations and classifications and has reduced the timeframes for taking compliance actions, even as the volume of compliance actions has increased. The percentage of cases in which CDER concurs with ORA's initial recommendation is known as the "concurrence rate." The concurrence rate has steadily increased over the last 10+ years, indicating a corresponding decrease reclassifications; concurrence rates on foreign drug inspections designated OAI were 50 percent in 1996 and rose to 73 percent in 2019.

Question. Do you have data on how many inspection reports have been reclassified by CDER? If not, why not? If so, will you commit to sharing that data with the committee?

Answer. Since ConOps was implemented, for FY18 and FY19, CDER received 351 classification recommendations from ORA. There were 74 downgrades (~25 percent of initial OAI recommendations) as well as 17 upgrades (~30 percent of initial NAI/VAI classifications).

Question. Please describe the factors CDER considers when reclassifying a finding from "Official Action Indicated" to a lower level.

Answer. Under the ConOps agreement, when ORA initially recommends classifying the inspection as OAI, CDER reviews the report along with any remediation plan or response submitted by the company. CDER evaluates the evidence supporting inspection observations, potential impact to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. CDER may reclassify the inspection based on this review. If CDER determines an enforcement action is not warranted, ORA is notified of the downgraded classification and provided a written description of the reason(s) for downgrade within 40 days. CDER may make this determination based on analyses that included evaluation of the evi-

[1] *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database*.

dence to support the inspection observations, the impact to patient safety, and the firms' responses to the observations and whether their proposed corrective actions were adequate.

Question. In light of the safety issues surrounding foreign drug manufacturing discussed during this and previous congressional hearings, is the FDA researching any alternative models of monitoring the drug supply chain? If so, please explain.

Answer. Several FDA proposals included in the FY 2021 President's Budget request would help the agency in its efforts to further strengthen the supply chain and address drug shortages. In particular, the request included the proposal, "Improving Critical Infrastructure Through Improved Data Sharing: Requiring More Accurate Supply Chain Information."

This proposal would help FDA better anticipate and react more expeditiously to drug shortages by enabling us to quickly identify all manufacturing sites impacted, analyze potential bottlenecks, and develop options to remediate shortage risks to the product supply chain. For example, having this information available would reduce the time FDA staff must spend to determine if a facility is the only facility distributing a drug product or API, or to determine which firms rely on an API supplier located in an area impacted by a natural disaster.

In addition, FDA works to improve its evaluation of the effectiveness of our inspection programs to ensure that our inspection capacity, procedures, and techniques are suitable in addressing the risks and challenges we face in ensuring drug quality for U.S. consumers.

FDA's Office of Regulatory Affairs (ORA) has an established quality management system (QMS) that aims to provide consistent investigational processes and work products, meet organizational requirements, and enable continual improvement of inspectional operations. The QMS ensures investigators can access procedures and instructions necessary to perform operational activities in a consistent manner, and provides a risk-based approach for capturing, analyzing, and addressing issues. The system includes quality control activities to review work products and quality assurance activities (such as audits and management reviews).

FDA also evaluates the significance of the findings from each inspection to assess the need for further regulatory activity to address non-compliance.

DRUG SHORTAGES

Question. In certain instances, the FDA has approved medication under Medicare and later discovered that manufacturers have not complied with relevant statutes and regulations. In those instances where withdrawing approval of a drug would create a shortage, does the FDA suspend approval of the drug until compliance is met? If not, what steps does the FDA take to bring the manufacturer back into compliance?

Does the FDA treat drug compliance enforcement action differently based on the scarcity of a drug?

Answer. FDA does not approve drugs specifically for or under Medicare; FDA approves drugs for the American public based on the safety and efficacy standards established in the Federal Food, Drug, and Cosmetic Act, and the Centers for Medicare and Medicaid Services (CMS) decides whether and how it will be covered in the programs they administer. However, below, we explain the coordination that occurs within FDA with respect to compliance actions and the potential for shortages of drugs subject to the shortage notification requirement in section 506C(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

As described in FDA's Drug Shortage Management Manual of Policies and Procedures (MAPP) *(https://www.fda.gov/media/72447/download)*, the Center for Drug Evaluation and Research's (CDER's) Office of Compliance works closely with the Drug Shortage Staff before taking any enforcement action or issuing a warning letter to determine if the action or letter could cause or exacerbate a drug shortage. If it is determined that an action or warning letter could lead to or exacerbate a shortage, the Office of Compliance works with the Drug Shortage Staff and other appropriate offices to evaluate the risks to patients associated with a potential shortage and the risks associated with the violation involved. As appropriate, the agency may then decide to exercise enforcement discretion, as a temporary measure, to help prevent or mitigate the potential shortage.

FDA has used temporary regulatory flexibility and discretion for the distribution of certain medically necessary products (as defined in the Drug Shortage Management MAPP) that present quality issues with measures to mitigate risk in light of the risk to patients of not receiving the drug, as follows: filters are supplied with a product to remove particulate matter; extra testing for product quality or identity is done at the manufacturing facility before releasing the product into the marketplace; third-party oversight of production is instituted to monitor quality issues; and special instructions are provided to health-care professionals/patients.

FDA has also exercised temporary regulatory flexibility and discretion with regard to continued distribution of a drug product to mitigate or resolve a drug shortage while FDA reviews a supplement/proposed change to address a problem with the drug product.

During a drug shortage, whether or not such mitigating measures are taken as a temporary measure, FDA's priority is to restore supplies of FDA-approved drugs that comply with applicable standards, and we use all of our authorities toward this end. This may include, for example, working with sponsors to resolve quality issues, expediting review of applications that could address a shortage, or seeking additional sources of a drug in shortage.

Question. What forms of non-compliance does the FDA consider to be material to the approval status of a drug?

Answer. FDA-approved drugs have been shown to be safe and effective under applicable provisions of the FD&C Act and its implementing regulations. To be legally marketed, approved drugs must meet all applicable legal requirements. *See generally* sections 501, 502, 503 and 505 of the FD&C Act (21 U.S.C. 351–53, 355). Approval may be withdrawn if the standard for withdrawing an approval is met. See section 505(e) of the FD&C Act (21 U.S.C. 355(e)); *see also* 21 CFR 314.150–153.

DRUG TESTING

Question. You testified that "only a small percentage, about 1 percent, of drugs that are tested [by FDA] fail to meet the established quality specifications."

How does the FDA commonly procure batches of pharmaceutical products for analysis?

If these products are procured directly from manufacturers, does this present the potential for fraud and abuse?

Describe FDA's programs, if any, to acquire medication samples without voluntary submission from manufacturers, including what percentage of the FDA's testing comes from such programs.

Answer. FDA has a long-standing program to regularly sample and test marketed drugs and active pharmaceutical ingredients (APIs) for conformance to specifications. We select hundreds of samples each year based on certain criteria.

- Some testing decisions are event-driven. For example, we might test product samples after receiving a pattern of complaints about adverse events, quality issues or reduced effectiveness. These reports come to FDA consumer complaints, field alert reports and MedWatch: The FDA Safety Information and Adverse Event Reporting Program.
- We also rely on the experience of internal and external experts to alert us to emerging safety, effectiveness, or quality issues with currently marketed drug products. For example, results from independent research may require FDA testing and investigation.

Sometimes, manufacturing or facility concerns may trigger additional FDA monitoring and testing. For instance, FDA may sample products with difficult manufacturing processes or drug products with complex dosage forms such as patches, drugs designed to target a specific area, and drugs that release the active ingredient in a controlled manner.

FDA may also sample drugs produced by manufacturing processes that require additional controls to assure each dosage unit will perform as expected, such as delivering a precise amount of active ingredient within a narrower range, because even slight deviations could cause quality issues.

We use a risk-based approach to quality testing. This means that in cases where there is a known or likely safety, effectiveness, or quality issue with a product, FDA scientists perform tests specifically for this vulnerability. For example, if an API is

likely to become contaminated with a harmful impurity during the manufacturing process, FDA tests for that specific impurity, rather than testing for all potential impurities.

Through our risk-based import screening tool, PREDICT (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting), FDA focuses agency import resources, including activities such as examinations and sample collections, on higher-risk products being offered for entry into U.S. commerce. PREDICT uses automated data mining, pattern discovery, and automated queries of FDA databases to determine the potential risk of a shipment. The analytics tool takes into consideration the inherent risk of a product and information about the previous history of importers, manufacturers, and shippers. As part of our COVID–19 response, FDA has adjusted PREDICT screening to account for firms whose foreign inspection was postponed due to COVID–19 travel restrictions.

FDA labs acquire samples for testing by a number of different mechanisms, including directly from consumers and purchases from the U.S. market via distributors, wholesalers, and retail pharmacies. FDA has found that approximately one percent of samples tested, both foreign and domestic, fail to meet quality standards. In addition, FDA investigators can collect the samples directly at drug manufacturing sites and deliver or send them to FDA testing labs (maintaining chain of custody). If required, FDA also has the ability to purchase samples online while retaining anonymity. Finally, some samples are sent to FDA labs directly from manufacturers as the result of information request (IR) letters from FDA assessor staff. In many cases, such samples are requested to verify test results on the same batches the firms supply to FDA. Using this "trust but verify" approach, the agency can use the most accurate available data to make regulatory decisions.

INDIA PILOT PROGRAM

Question. In 2013 the FDA implemented the India Pilot Program that eliminated announced inspections or provided a couple days' worth of notice, instead of weeks. The result was an increase in the FDA's most serious finding, "Official Action Indicated."

This pilot program was shut down in 2015 by the Obama administration without explanation and FDA returned to the previous practice of announcing inspections.

Do any of you know why the Obama administration shut down the India Pilot Program?

Who at the FDA made the decision to end the India Pilot Program?

Would you describe the pilot program as a success? If not, why not?

What lessons have you learned from the program that have been implemented into FDA practices today?

Answer. FDA's Office of International Programs, in collaboration with FDA's Office of Regulatory Affairs, conducted an initiative between January 2014 and August 2015 to reduce the notification time for a drug inspection in India to one business day or less. This initiative (often referred to as a pilot) allowed for the utilization of in-country FDA and State Department resources for logistics (*e.g.,* visa invitation letters, hotel reservations).

In August 2015, FDA decided not to extend the initiative due to the following: (1) the lack of a sufficient protocol and evaluation criteria for such an initiative limited to a single country and (2) the need to analyze the dataset generated during the initiative up until that point in order to consider its impact on agency resources, on industry operating within India, and on other aspects of FDA's foreign inspections program. At this time, FDA is evaluating establishing criteria to assess unannounced inspections in the foreign arena.

As we have stated, the inspection initiative in India was not a true "pilot," but we have implemented some best practices that we determined were useful from our experiences with the initiative. First, we stopped having firms issue letters so that we could get visas for our investigators. We also no longer have firms involved in making hotel selections or help with other travel arrangements. Finally, we began a program where the investigator receives a pre-inspection briefing from his or her colleagues at ORA headquarters to improve the efficiency and effectiveness of the inspection.

SUPPLY CHAIN VISIBILITY

Question. According to testimony from the FDA in October 2019, the FDA "has no visibility into which active pharmaceutical ingredient supplier a final dosage form manufacturer uses at any given time." Should FDA have that type of visibility to better ensure quality and safety? If not, why not?

Answer. Yes, it is important for FDA to have this information to ensure quality and safety because the lack of adequate information on the identity of sites involved in the manufacture of drugs, including API suppliers, for U.S. consumers makes it difficult for FDA to identify the scope of products that could be implicated, should a problem arise.

In 2017, because this information was not readily available, FDA had to expend significant resources to gather this critical distribution and supply chain information to address supply disruptions caused by the multiple hurricanes in Puerto Rico. This lack of adequate insight is particularly an issue with respect to foreign sites as well as manufacturers of API used in non-application drugs, such as over-the-counter (OTC) monograph drugs, (*i.e.,* those for which marketing is governed by 505G of the FD&C Act). At least with respect to products with approved applications, we have some insight into which API sources may be used by the FDF facilities.

All domestic finished dosage form (FDF) and API establishments are required to register with FDA, and all foreign FDF and API establishments that manufacture drugs (including APIs) that are imported or offered for import into the United States are required to register with FDA. However, some foreign API and FDF establishments that ship to other foreign establishments prior to the drugs being imported or offered for import into the United States currently do not register with FDA. Ensuring that all foreign establishments involved in the manufacturing of drugs for the U.S. market register with FDA is important because, among other things, our risk-based inspection paradigm is based on establishment registration.

Additionally, API intermediate facilities (foreign or domestic) are not currently required to register with FDA. The lack of registration of a portion of the drug supply chain leaves the agency with significant blind spots when working to predict, mitigate, and address drug shortages. Without sufficient insight into the upstream supply chain for drug products, the agency is often unaware of whether an event affecting a particular country or region could potentially disrupt the U.S. drug supply, and unable to conduct appropriate oversight of potential risks in the drug supply chain.

Clarifying that registration is required for all foreign establishments involved in manufacturing drugs for the U.S. market and expressly requiring the registration of API intermediate establishments would close a major information gap and help to prevent foreign manufacturers from introducing unsafe drugs into the U.S. supply chain. FDA is requesting explicit statutory authority along these lines so that we can expeditiously collect critical distribution and supply chain information and more rapidly improve our ability to address the critical public health issue of drug shortages before the next natural disaster or unforeseen hazard impacts U.S. patients.

Question. What has the FDA done to solve these limitations? Please describe in detail what FDA could do to shore up these limitations and provide greater visibility into the drug supply chain.

Answer. On March 27, 2020, the President signed into law, the "CARES Act," Pub. L. 116–136. Among the provisions included was a requirement added to the FD&C Act that manufacturers annually report to FDA on the "amount of each drug . . . that was manufactured, prepared, propagated, compounded, or processed" for commercial distribution.

FDA is leveraging this reporting requirement under the CARES Act so that registered drug establishments will submit data in a uniform format regarding the volume of APIs and finished dosage forms manufactured at each registered facility. However, the volume data reporting provided for in the CARES Act did not include the level of detail needed for FDA to accurately assess our reliance on certain countries to supply APIs for drugs manufactured for distribution in the United States.

During consideration of legislation ultimately enacted as the CARES Act, FDA proposed a more extensive set of policy priorities for inclusion in the legislation, and still maintains that these policies would position the agency to better predict and mitigate drug shortages. These policies were included in the FY 2021 President's

Budget and propose to require more detailed and timely information about a product's current supply chain and distribution to help the agency better anticipate and react more expeditiously to drug shortages. The additional information would enable us to quickly identify all manufacturing sites impacted, analyze potential bottlenecks, and develop options to remediate shortage risks to the product supply chain. For example, having this information available would reduce the time FDA staff must spend to determine if a facility is the only facility distributing a drug product or API, or to determine which firms rely on an API supplier located in an area impacted by a natural disaster.

Specifically, this President's Budget proposal was titled, "Improving Critical Infrastructure Through Improved Data Sharing: Requiring More Accurate Supply Chain Information." This proposal, if enacted, would ensure that each FDF facility, API facility, and API intermediate facility is registered with FDA, including foreign facilities that manufacture products that are indirectly imported into the United States. Additionally, the proposal would require regular (quarterly) reporting of certain disaggregated manufacturing volume data and supply chain information. Specifically, FDF establishments would be required to provide information about the volume of each drug manufactured for the U.S. market, including the source and amount of API from each source used to manufacture the FDFs. API establishments would be required to provide information about the volume of API manufactured for the U.S. market, including the source and amount of API intermediate from each source used to manufacture the APIs.

Question. What risks to the drug supply chain have been exposed and/or increased during the COVID–19 pandemic? What has FDA done to bring solutions to mitigate those risks?

Answer. At this time, FDA is aware that there is an acute demand for certain products and disruptions in the supply chain due to COVID–19, and we are taking proactive steps to make sure that patients can access the medications that are medically appropriate and necessary. We work with our Federal partners, industry, professional organizations, and other stakeholders to identify and address supply chain issues. FDA provides technical assistance to other Federal agencies that are seeking to prevent and mitigate supply chain disruptions and are considering a variety of solutions including increasing U.S. manufacturing when possible. We are also working closely with stakeholders to establish mitigation strategies and prevent long-term supply shortages.

We work closely with manufacturers to make sure they continue to notify FDA, as early as possible, of a permanent discontinuance or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply to the extent required under section 506C of the FD&C Act. This communication and the full cooperation of companies providing specific and necessary information is imperative for us to have an accurate understanding of the supply landscape and work to take proactive steps to mitigate shortages. To help human drug manufacturers submit timely and informative notifications, the agency published a guidance[2] in March about these notifications, the timelines that manufacturers should follow when notifying FDA, and the details they should provide about the discontinuance or interruption of manufacturing. We recognize that although some supply disruptions and shortages cannot be predicted or prevented, early communication and detailed notifications from manufacturers to the agency play a significant role in decreasing their incidence, impact, and duration.

FDA's public drug shortages lists are up-to-date with human[3] and animal[4] drugs and biological products[5] that we have determined to be in shortage. These shortages are not all the result of COVID–19, with many existing prior to the public health emergency as the result of market changes and supply challenges. We are updating these lists regularly and communicating in real-time so that patients and healthcare providers have the most current information on product shortages in the United States.

The pharmaceutical sector relies heavily on foreign sourcing for critical components, materials, and finished products. However, use of foreign-sourced materials

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[2] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-permanent-discontinuance-or-interruption-manufacturing-under-section-506c-fdc-act*.
[3] *https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm*.
[4] *https://www.fda.gov/animal-veterinary/product-safety-information/current-drug-shortages*.
[5] *https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages*.

can create vulnerabilities in the U.S. drug supply chain as evidenced by the COVID–19 public health emergency.

In response to the presidential executive order on Buy American and Hire American (EO 13944), FDA is identifying those essential medicines, medical countermeasures, and critical inputs that are essential to have available at all times. Additionally, FDA continues its efforts to facilitate that use of advanced manufacturing because FDA believes that advanced manufacturing technologies could enable U.S.-based pharmaceutical manufacturing to regain its competitiveness with foreign countries, and potentially ensure a stable supply of drugs critical to the health of U.S. patients. Advanced manufacturing offers many advantages over traditional pharmaceutical manufacturing, and if the United States invests in this technology, it can be used to reduce the Nation's dependence on foreign sources of active pharmaceutical ingredients (APIs), increase the resilience of our domestic manufacturing base, and reduce quality issues that trigger drug shortages or recalls.

In FY 2020, FDA's Center for Drug Evaluation and Research received $9M of one-time, supplemental funding that will be used to continue to modernize and enhance science in areas related to advanced pharmaceutical manufacturing. Knowledge generated from these activities, together with the information provided by sponsors or applicants, could help enable science- and risk-based assessment and inspection; establish best assessment and inspection practices; support standard, policy and guidance development; and provide important training on novel manufacturing technologies.

All domestic finished dosage form (FDF) and API establishments are required to register with FDA, and all foreign FDF and API establishments that manufacture APIs or FDFs that are imported or offered for import into the United States are also required to register. However, some foreign API and FDF facilities that ship to other foreign facilities prior to the drugs reaching the United States currently do not register with FDA.

Foreign or domestic facilities producing API intermediates are not required to register with FDA. (An API intermediate is a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API.) The lack of registration of a portion of the drug supply chain leaves the agency with significant blind spots when working to predict, mitigate, and address drug shortages. Without sufficient insight into the upstream supply chain for drug products, the agency is unaware of whether an event affecting a particular country or region could potentially disrupt the U.S. drug supply, and is unable to effectively conduct appropriate oversight of potential risks in the drug supply chain. This is particularly the case for APIs used in non-application products (such as over-the-counter (OTC) monograph drugs, *i.e.,* those marketed under section 505G of the FD&C Act) because, at least with respect to products with approved applications, we have some insight into which API sources may be used by the FDF facilities as part of the application assessment process.

Additionally, there are importers that appear to be registering manufacturers without their knowledge. As a result, when the agency identifies that a potentially hazardous product is in the market or at the border pending evaluation, our investigation and discussion with the importer and manufacturers are unnecessarily delayed while we work to determine the facts of the case, the responsible parties, and the most effective path to minimize harm to consumers and patients.

Another important challenge discussed in the hearings concerns our oversight of APIs and FDFs coming into the United States, including non-sterile and sterile drugs that do not require an application to be marketed, such as APIs for compounding, and APIs for OTC monograph drugs as well as FDFs of such drugs. For such drugs not subject to premarket approval requirements, manufacturers may not be inspected by FDA before such products are shipped to or distributed in the United States. FDA can take action if we become aware of a quality problem with these drugs; however, patients may have already been exposed to the drugs. Compounding this problem, if the agency identifies problems with the facilities after the drugs are already on the market, the agency lacks authority to mandate recalls for most drugs.

Question. What percent of total volume of API used to make pharmaceuticals intended for the U.S. market comes from China? Please answer the same with respect to India.

Answer. For the reasons described in more detail below, we are unable to provide data on the percent of total volume of APIs used to make pharmaceuticals intended

for the U.S. market that comes from China or India. The best data we are able to provide are the percent of registered API manufacturers in these countries.

- As of May 2020, 13 percent of the API facilities that supply all product types to the United States were located in China.
- As of May 2020, 19 percent of the API facilities that supply all product types to the United States were located in India.

Prior to enactment of the CARES Act on March 27, 2020, registered drug establishments were not required to submit consistent data regarding the volume of APIs and finished dosage forms manufactured at each registered facility. The CARES Act imposed annual volume data submission requirements on all drug establishments registered with FDA (section 510(j)(3) of the FD&C Act).

During consideration of the CARES Act, FDA proposed a more extensive set of legislative enhancements, reflecting the agency's policy priorities, and still maintains that these policies would provide the agency with more information about drug supply chains, bolstering our ability to predict, prevent, and mitigate shortages. The key elements of this proposal are to amend the FD&C Act to:

- Ensure that each finished dosage form (FDF) facility, API facility, and API intermediate facility is registered with FDA, including foreign facilities that manufacture products that are indirectly imported into the United States (*i.e.,* used in foreign manufacturing of drug products that are subsequently shipped to the U.S.); and
- Require regular (quarterly) reporting of certain disaggregated manufacturing volume data and supply chain information. Specifically, FDF establishments would be required to provide information about the volume of each drug manufactured for the U.S. market, including the source and amount of APIs from each source used to manufacture the FDFs. API establishments would be required to provide information about the volume of APIs manufactured for the U.S. market, including the source and amount of API Intermediate from each source used to manufacture the APIs.

However, the additional volume data provided for in the CARES Act did not include this level of detail and limits our ability to accurately assess our reliance on certain countries to supply APIs for drugs manufactured for the United States.

Question. What percentage of registered fine chemical facilities used in the production of API for pharmaceuticals intended for the U.S. market are located in China, and what percent of total volume of fine chemicals used to make API for pharmaceuticals intended for the U.S. market come from China? Please answer the same with respect to India.

Answer. We are unable to provide this information because as noted above, manufacturers of fine chemicals (what we generally refer to as API intermediates) are not required to register with FDA, and API manufacturers are not required to provide FDA with information about the extent of their reliance on their sources of API intermediates. FDA has asked for express statutory authority to begin collecting this information.

The CARES Act imposed annual volume data submission requirements on all drug establishments registered with FDA (section 510(j)(3) of the FD&C Act). However, it did not require the submission of certain disaggregated volume data regarding drugs produced by API and FDF establishments, such as information about the sources of APIs and API intermediates, nor about the amount of APIs and finished dosage forms manufactured from each source. Additionally, the CARES Act did not impose registration or listing requirements on fine chemical (API intermediate) manufacturers.

NATIONAL SECURITY

Question. Please describe the relationship that each of your units has with the Office of National Security within the Department of Health and Human Services.

Answer. FDA's Office of Global Policy and Strategy (OGPS) has a strong relationship with the Office of National Security (ONS) within the Department of Health and Human Services. When appropriate, OGPS leadership receives classified briefings from ONS, including briefings related to counterintelligence. OGPS leadership also receives a weekly unclassified briefing document from ONS. OGPS shares information generated at headquarters as well as at the FDA foreign offices with ONS when relevant.

CDER engagement with other Agencies focused on national security is coordinated through the Office of Counter-Terrorism and Emerging Threats (OCET) in the Office of the Commissioner. Through them, we have extensive contacts on matters relating to drug manufacturing and the integrity of the supply chain.

Question. Please describe the steps that you will take to create a better relationship between your units and the Office of National Security. If such a relationship is not needed, please explain why that is the case.

Answer. Currently OGPS engages with ONS when a specific situation requires it to do so. OGPS plans to establish regular meetings with ONS to discuss issues of mutual interest. OGPS will work with ONS to determine the frequency of such meetings.

CDER engagement with other Agencies focused on national security is coordinated through the Office of Counter-Terrorism and Emerging Threats (OCET) in the Office of the Commissioner. Through them, we have extensive contacts on matters relating to drug manufacturing and the integrity of the supply chain.

Question. Please describe the national security risks that China presents to the drug supply chain.

Answer. As a sole source for certain essential pharmaceuticals, such as crude heparin, antibiotics, essential APIs and API starting materials/critical intermediates, China presents as a vulnerability and security risk to the U.S. drug supply chain. This has been made clear earlier in 2020 as China's role as a major U.S. and global supplier of certain medical products led to shortages of critical medical supplies during the COVID–19 pandemic.

The following is a list of potential conditions that could lead to further security risks. The list is broken out by short-term/less predictable risks and long-term/government policy- or trade-related risks.

Short-Term Risks:

- Unexpected supply chain disruptions (*e.g.,* COVID–19, flooding, shutdowns, explosions).
- In the event of a natural disaster or pandemic, requirements in China to focus on domestic supply, limiting exports to countries like the United States.
- Introduction of falsified or substandard products into the supply chain.
- Diversion of the supply chain within China or shipping from China to an alternate location before arriving in the United States.

Longer-Term Risks:

- Politically motivated shutdown of exports from China.
- Politically motivated price controls by China.
- Lack of intellectual property protection of innovative products.
- Subsidies given to domestic firms in China causing an imbalance in competition, driving foreign companies out of the market.

QUESTIONS SUBMITTED BY HON. JOHN CORNYN

SUPPLY CHAIN TRANSPARENCY

Question. Congress took important action as part of the Coronavirus Aid, Relief, and Economic Security (CARES) Act (H.R. 748) enacted in March. The CARES Act includes several important steps intended to help strengthen the pharmaceutical supply chain. Specifically, section 3112 of the CARES Act increases the transparency of the pharmaceutical supply chain by providing FDA with additional information on potential disruptions in the supply chain, on manufacturers' contingency plans to ensure continued supply and on the volume of medicines manufactured.

FDA was provided with 180 days to implement these new requirements. What is FDA's plan for issuing guidance and ensuring these provisions are implemented in a timely manner?

Answer. The CARES Act amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require that manufacturers provide FDA with certain information about permanent discontinuances and interruptions in manufacturing of finished products and active pharmaceutical ingredients (APIs). In addition, the CARES Act amended the FD&C Act to require that manufacturers develop, maintain, and implement, as appropriate, a redundancy risk management plan for certain drugs,

APIs, and associated devices. These requirements took effect on September 23, 2020. FDA staff are working to issue guidance for industry to assist manufacturers in complying with these new requirements.

The CARES Act also includes authorities that enhance FDA's ability to identify, prevent, and mitigate possible drug shortages by, among other things, enhancing FDA's visibility into drug supply chains. Specifically, section 3112(e) amends the FD&C Act to require that each registered drug establishment annually report the "amount of each drug . . . that was manufactured, prepared, propagated, compounded, or processed" by the registrant for commercial distribution. This CARES Act amendment also provides that such "information may be required to be submitted in an electronic format."

FDA staff are working to define the data to be reported, create an electronic portal for the submission of this information, and determine when to begin collecting this information. We will provide further updates as our implementation planning continues.

ACTIVE PHARMACEUTICAL INGREDIENT TESTING

Question. Before active pharmaceutical ingredients (APIs) are used in finished dosage form manufacture, are they generally tested?

Answer. Current regulations require drug product manufacturers to test all components (ingredients) before use in manufacturing. Manufacturers are required to test representative samples of each lot of drug product before releasing the product to market. Testing requirements also include testing raw materials and API batches before use and, where appropriate, testing during the processing of APIs and final products. Generally during CGMP inspections, we review the records that manufacturers must maintain regarding required testing, including testing for the expected and controlled impurities and degradation compounds.

Question. Mr. Abdoo, testimony states that FDA has conducted more foreign inspections than domestic since 2015.

Is there a focus on facilities that produce final dosage forms (FDFs) over active pharmaceutical ingredients (APIs)?

Answer. Any facility that registers their establishment in FDA's electronic drug registration and listing system (eDRLS) is subject to an inspection as soon as possible following initial registration. If the establishment is only associated with a pending NDA, ANDA, or BLA, FDA may conduct a pre-approval facility evaluation and inspection as part of the application assessment process. If the application is approved, all manufacturing facilities identified in the approved application that are required to register annually with FDA will be included in CDER's Catalog of Manufacturing Sites and will be subject to a surveillance inspection on a risk-based schedule in accordance with section 510 of the FD&C Act.

FDA has a publicly available Manual of Policies and Procedures (MAPP) 5014.1 that describes the agency's risk-based approach to prioritizing and scheduling manufacturing sites for CGMP surveillance inspections. One goal of this approach is to achieve parity in inspection frequency, meaning equal frequency for sites with equivalent risk, regardless of geography (foreign versus domestic). API and FDF facilities are prioritized for inspection in accordance with the same Site Selection Model.

Question. If a foreign facility is subject to a for-cause inspection, are facilities that source their products notified, and what is the procedure for doing so?

Answer. No, firms that source products from companies that undergo a for-cause inspection are not notified of the inspection. FDA considers a for-cause inspection to include: (i) follow-up compliance inspections performed to verify corrective actions after a regulatory action has been taken; (ii) inspections performed in response to specific events or information (Field Alert Reports (FARs)), Biological Product Defect Reports (BPDRs), industry complaints, recalls, and other indicators of defective products, etc.) that bring into question the compliance and/or quality of a manufacturing practice, facility, process, or drug.

Follow-up compliance inspections provide focused coverage and include the areas of concern, the proposed corrective action plan for impacted operations, any implemented corrective actions, and/or the deficiencies noted on the Form FDA 483.

PHARMACEUTICAL PRODUCT TESTING

Question. What percentage of drugs that are sampled and tested by FDA fail to meet the established quality specifications?[6]

Do the products that fail tend to be domestically manufactured?

Answer. FDA has found that approximately one percent of samples tested, both foreign and domestic, fail to meet quality standards. As noted in a recent *JAMA* article authored by FDA scientists, difficult-to-make prescription pharmaceuticals marketed in the U.S. consistently meet quality standards whether they are manufactured in the United States or elsewhere. Please see *https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2769690.*

FOCUS ON CHINA AND INDIA

Question. In recent years, the agency has prioritized India and China with respect to inspections. This inspectional emphasis is further supported by the facts that China and India account for 13 percent and 18 percent of the global API manufacturing, respectively. However, the U.S. and EU still account for 28 percent and 26 percent of the global API manufacturing.

Can you discuss the factors that FDA considers when prioritizing inspections in certain countries?

Answer. The agency utilizes a risk-based mathematical model, the Site Selection Model (SSM), to select facilities with the greatest potential for public health risk should they not comply with established manufacturing quality standards. FDA uses results of the model to prepare a prioritized list of facilities for inspection from its Catalog of Manufacturing Sites. Factors in the SSM include inherent product risk, facility type, patient exposure, inspection history, time since last inspection, and hazard signals. FDA compares a facility's score to others in the Catalog of Manufacturing Sites and ranks them by risk, with the highest risk assigned for inspection regardless of location (foreign versus domestic).

Question. In 2013, FDA created the India Pilot Program that eliminated the practice of advanced notice inspections and implemented short notice or unannounced examinations of Indian drug manufacturing. The new inspection program exposed numerous safety issues and FDA issued a nearly 60 percent increase in Official Action Indicated findings. The program was shut down in 2015.

Has FDA applied any lessons learned from the India Pilot Program in their approach to foreign inspections since 2015?

Answer. We have implemented some best practices that we determined were useful from our experiences with the initiative. First, we stopped having firms issue letters so that we could get visas for our investigators. We also no longer have firms involved in making hotel selections or help with other travel arrangements. And finally, we began a program where the investigator receives a pre-approval briefing from his or her colleagues at ORA headquarters to improve the efficiency and effectiveness of the inspection.

ACCESS TO TRANSLATORS FOR FOREIGN INVESTIGATORS

Question. GAO found that FDA was not generally providing translators on foreign inspections and was relying on those provided by the establishments being inspected.

Does FDA provide guidelines to foreign facilities for the qualifications of the translators they provide?

Answer. No, FDA does not have formal guidelines for the qualifications of translators present at inspections. FDA's current practice is to use firm personnel for interpreter/translation services when possible. If firm personnel do not primarily speak English, FDA will use other sources, such as FDA staff fluent in the language appropriate to the inspection or using an agency-contracted interpreter through an Interagency agreement with the U.S. Department of State.

Question. Do you believe there could be a conflict of interest when the establishment being investigated is employing the translator?

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[6] Only about 1 percent of drugs that are tested fail to meet quality specifications (*http://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019).*

Answer. At this time, we rely on information provided by the firm during all inspections, including those inspections in the United States. As mentioned earlier, investigators are skilled to detect inconsistencies in data. We currently do not have data to show that firm translation activities have negatively impacted the accuracy of information provided. We do intend to evaluate this issue and had planned a study to evaluate using our own translation services; this has been delayed due to the current public health emergency.

QUESTIONS SUBMITTED BY HON. PATRICK J. TOOMEY

Question. How did the FDA gather the information necessary to make the following statement in March posted to its website: "The FDA has identified about 20 other drugs, which solely source their active pharmaceutical ingredients (API) or finished drug products from China. We have been in contact with those firms to assess whether they face any drug shortage risks due to the outbreak. None of these firms have reported any shortage to date. Also, these drugs are considered non-critical drugs."

Answer. FDA conducted a resource-intensive data analysis to gather this information. We used multiple FDA sources that maintain data on approved application products (New Drug Application (NDA), Abbreviated New Drug Application (ANDA), and Biologics License Application (BLA)) and sites. These data sources include the Orange Book, CDER Product and Site Catalogs, CDER Informatics Platform (Integrity and Panorama), Document Archiving, Reporting and Regulatory Tracking System (DARRTS), and Electronic Drug Registration and Listing Systems (EDRLS). In addition, information was extracted from application forms (356H PDF files) submitted by applicants for changes in manufacturing facilities linked to applications to verify data accuracy. To identify facilities, the data used include the FDA Establishment Identifier (FEI), Data Universal Numbering System (DUNS), and location of facility. FDA contacted firms, as appropriate, to make assessments about potential impacts. Despite our rigorous process to gather this information, there continue to be gaps in the visibility that FDA has into foreign supply chains.

Question. Did the FDA gather information on drugs either solely made or API solely sourced in any other countries? If not, why? If so, what is the comparable data from those other countries?

Answer. In February 2020, FDA conducted sole source analysis to identify drugs whose APIs and/or FDFs were only available from China. As the outbreak spread, we began to focus on other impacted and potentially impacted countries, such as India, Italy, and the Republic of Korea. However, the outbreak quickly became a global pandemic and there were many impacted countries. At that point, our analysis changed from focusing on individual countries to focusing on drugs deemed essential and their global supply chain with any vulnerabilities.

Question. Can the FDA perform a broader review of drugs that are either solely made or contain an API solely sourced outside of the U.S. and provide this information on a monthly basis to the public?

Answer. We monitor all drugs with the potential for shortage, including those products which are sole source. Any of these products that do fall into shortage are then posted to FDA's shortage list and closely monitored, and their status is regularly updated on the drug shortage website.

Question. What are the primary reasons for drug shortages during the COVID–19 pandemic?

Answer. The primary reasons for drug shortages during the COVID–19 public health emergency are basically two-fold: (1) Increased demand for certain drugs to treat patients with COVID–19; and (2) drug supply chain disruptions. For the latter, supply chain problems can result from interruptions in manufacturing that may be caused by disruptions in supply of ingredients, labor shortages, or quality problems.

Question. Was the information required of manufacturers in the CARES Act enough (it required manufacturers to report volume of particular medicines by manufacturing site) or is more data needed for FDA to fully and accurately determine which drugs have particularly vulnerable supply chains?

Answer. The additional volume data provided for in the CARES Act does not include enough detail to enable FDA to accurately assess reliance on certain countries to supply APIs for drugs manufactured for the United States. The CARES Act imposed annual volume data submission requirements on all drug establishments reg-

istered with FDA (section 510(j)(3) of the FD&C Act). However, it did not require the submission of certain disaggregated volume data regarding drugs produced by API and FDF establishments, such as information about the sources of APIs and API intermediates, nor about the amount of APIs and finished dosage forms manufactured from each source. Additionally, the CARES Act did not impose registration or listing requirements on manufacturers of API intermediates.

During consideration of the CARES Act, FDA proposed a more extensive set of legislative enhancements, reflecting the agency's policy priorities, and still maintains that these policies would provide the agency with more information about drug supply chains, bolstering our ability to predict, prevent, and mitigate shortages. The key elements of this proposal are to amend the FD&C Act to:

- Ensure that each finished dosage form (FDF) facility, API facility, and API intermediate facility is registered with FDA, including foreign facilities that manufacture products that are indirectly imported into the United States (*i.e.,* used in foreign manufacturing of drug products that are subsequently shipped to the U.S.); and
- Require regular (quarterly) reporting of certain disaggregated manufacturing volume data and supply chain information. Specifically, FDF establishments would be required to provide information about the volume of each drug manufactured for the U.S. market, including the source and amount of APIs from each source used to manufacture the FDFs. API establishments would be required to provide information about the volume of APIs manufactured for the U.S. market, including the source and amount of API Intermediates from each source used to manufacture the APIs.

Question. Given a large percentage of API manufacturers are located outside of the U.S., what are the options for increasing data reporting? Has FDA engaged with their European counterparts and other internal regulatory bodies to triangulate data on API? Is there information that other regulatory bodies are requiring or collecting that could or should be shared to provide a more complete picture of potential API dependence on other countries?

Answer. FDA participates in the International Active Pharmaceutical Ingredient Inspection Programme[7] that began operating in 2008. The international collaboration allows FDA to work with the European Medicines Agency (EMA), European Union (EU) authorities, the European Directorate for the Quality of Medicines (EDQM), Australia's Therapeutic Goods Administration (TGA), Health Canada, the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), and the World Health Organization (WHO) to share information on good manufacturing practice (GMP) inspections of manufacturers of APIs that are located outside of the participating countries. These facilities are largely in India, China, Mexico, and southeast Asia.

In 2018, the group published the Report on the International Active Pharmaceutical Ingredient Inspection Programme 2011—2016.[8] Over 6 years, 1,333 inspections were carried out at 458 manufacturing sites of common interest. These sites were located in 18 different countries, most of them in India (49 percent) and China (36 percent). Although the group focuses on site-level information, they often discuss product-level data as needed. The collaboration is ongoing.

Additionally, FDA relies on our Mutual Recognition Agreements (MRA) with the EU and confidentiality agreements that we have in place with other foreign countries with comparable inspectorates to share information from drug inspections conducted within each other's borders. A full list of countries with whom we have these agreements can be found on FDA's website.[9] MRAs are a tool FDA employs during the COVID–19 pandemic when FDA has not been able to conduct onsite inspections.

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[7] *https://www.ema.europa.eu/en/news/increasing-oversight-api-manufacturing-through-international-collaboration*.

[8] *https://www.ema.europa.eu/en/documents/report/report-international-active-pharmaceutical-ingredient-api-inspection-programme-2011-2016_en.pdf*.

[9] *https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra*.

QUESTIONS SUBMITTED BY HON. TODD YOUNG

DEPENDENCE ON CHINA/INDIA FOR APIS

Question. According to FDA's own data, the number of registered facilities making active pharmaceutical ingredients (APIs) in China more than doubled between 2010 and 2019—and according to Dr. Woodcock, the Director of FDA's Center for Drug Evaluation and Research, the "increasing number of API manufacturing sites in China and other countries suggests that the United States' reliance on Chinese and other foreign sources of API is growing."

How dependent are we on China, India, or other countries for the APIs used in drugs produced for patients in the United States?

Answer. As of May 2020, the breakdown of facilities manufacturing APIs for human drugs in the U.S. market are as follows:

Country or Region	Percent of API Manufacturing Facilities
United States	26
European Union	26
India	19
China	13
Canada	2
Rest of world	14

This does not include data on the volume of APIs manufactured, but rather the number of sites actively manufacturing APIs.

Prior to enactment of the CARES Act on March 27, 2020, registered drug establishments were not required to submit consistent data regarding the volume of APIs and finished dosage form drug products manufactured at each establishment. However, the CARES Act imposed annual volume data submission requirements on all drug establishments registered with FDA (section 510(j)(3) of the FD&C Act).

Question. Through the COVID pandemic, what risks have been exposed by China's increasing manufacturing presence?

Answer. Response included in the answer to the question below.

Question. Is it the FDA's assessment that we would improve our healthcare in the U.S. and increase our resiliency in future pandemics by decreasing our reliance on China's manufacturing these drugs?

Answer. Redundancy and geographic diversity are important keys to ensuring a robust drug supply chain. Manufacturers that have multiple establishments in different geographic regions have more resilient supply chains. A manufacturer's supply chain is even more resilient if the manufacturer sources its active pharmaceutical ingredients (APIs) from multiple, geographically diverse sources. The resiliency lies in the fact that if a natural disaster or disease outbreak affects establishments or suppliers in one geographic region, or one of its suppliers leaves the market, the manufacturer can utilize other establishments not affected by the natural disaster or outbreak or can source the API from one of its other suppliers.

However, FDA cannot prevent manufacturing concentration or require redundancy of manufacturing capability and capacity. Nor can FDA require a company to manufacture a drug, maintain a certain level of inventory of drug product, or reverse a business decision to cease manufacturing. We note that the CARES Act amended the FD&C Act to require manufacturers of certain drugs, APIs, and associated medical devices to develop, maintain, and implement, as appropriate, redundancy risk management plans, and FDA recommends that manufacturers of all drugs and APIs do so. Such plans can include opportunities for building redundant manufacturing capacity, holding spare capacity, or increasing inventory levels to lower the risks of shortages; and other stakeholders might explore how to incentivize such practices.

DATA LIMITATIONS

Question. According to the Director of FDA's Center for Drug Evaluation and Research's (CDER) October 2019 Testimony, there are significant data limitations relating to manufacturing facilities making drugs for the U.S. market—one being that we "cannot determine with any precision the volume of API that China is actually producing, or the volume of APIs manufactured in China that is entering the U.S. market, either directly or indirectly by incorporation into finished dosages manufactured in China or other parts of the world."

What has the FDA done to address these limitations?

Answer. The CARES Act imposed annual volume data submission requirements on all drug establishments registered with FDA (section 510(j)(3) of the FD&C Act). FDA has leveraged data required under the CARES Act for registered drug establishments to submit consistent data regarding the volume of APIs and finished dosage forms manufactured at each registered facility. The CARES Act did not require the submission of certain disaggregated volume data regarding drugs produced by API and FDF establishments, such as information about the sources of APIs and API intermediates, nor about the amount of APIs and finished dosage forms manufactured from each source. Additionally, the CARES Act did not impose registration or listing requirements on fine chemical (API intermediate) manufacturers. The additional volume data provided for in the CARES Act did not include information needed for FDA to accurately assess our reliance on certain countries to supply APIs for drugs manufactured for the United States.

Question. What needs to be done?

Answer. The additional volume data provided for in the CARES Act does not include enough detail to enable FDA to accurately assess reliance on certain countries to supply APIs for drugs manufactured for the United States. The CARES Act imposed annual volume data submission requirements on all drug establishments registered with FDA (section 510(j)(3) of the FD&C Act). However, it did not require the submission of certain disaggregated volume data regarding drugs produced by API and FDF establishments, such as information about the sources of APIs and API intermediates, nor about the amount of APIs and finished dosage forms manufactured from each source. Additionally, the CARES Act did not impose registration or listing requirements on manufacturers of API intermediates.

During consideration of the CARES Act, FDA proposed a more extensive set of legislative enhancements, reflecting the agency's policy priorities, and still maintains that these policies would provide the agency with more information about drug supply chains, bolstering our ability to predict, prevent, and mitigate shortages. The key elements of this proposal are to amend the FD&C Act to:

- Ensure that each finished dosage form (FDF) facility, API facility, and API intermediate facility is registered with FDA, including foreign facilities that manufacture products that are indirectly imported into the United States (*i.e.,* used in foreign manufacturing of drug products that are subsequently shipped to the U.S.); and
- Require regular (quarterly) reporting of certain disaggregated manufacturing volume data and supply chain information. Specifically, FDF establishments would be required to provide information about the volume of each drug manufactured for the U.S. market, including the source and amount of API from each source used to manufacture the FDFs. API establishments would be required to provide information about the volume of APIs manufactured for the U.S. market, including the source and amount of API Intermediates from each source used to manufacture the APIs.

QUESTIONS SUBMITTED BY HON. RON WYDEN

Question. On March 28, the FDA issued an Emergency Use Authorization (EUA) allowing the Strategic National Stockpile (SNS) to distribute chloroquine phosphate that was not approved by FDA for any indication, and hydroxychloroquine for COVID–19 treatment. The EUA also waived requirements Good Manufacturing Practices (GMP) otherwise applicable to the manufacture, processing, packing, or

holding of the drugs.[10] The EUA authorized receipt of hydroxychloroquine from Bayer originating from uninspected manufacturing facilities in Pakistan. A second company, IPCA Laboratories Ltd., manufacturing the drug, and reportedly donating 50 million tabs, has been on the FDA Import Alert list since 2015, but is now been allowed to export hydroxychloroquine sulfate and chloroquine phosphate to the U.S.[11]

Please list all facilities that were allowed to import chloroquine and hydroxychloroquine into the United States pursuant to the EUA, noting those that were had CGMP requirements waived.

Answer. Authorization was given to import donated chloroquine phosphate tablets into the United States twice, as follows:

First Donation of One Million Chloroquine Phosphate Tablets (Original EUA)

API Facility:
IPCA Laboratories Limited (CGMP requirements were waived)
89A–B/90/91
Industrial Estate
PoloGround, Indore—452003
India

Finished Drug Product Facility:
IPCA Laboratories LTD (Unit–I) (CGMP requirements were waived)
C–6, Sara industrial Estate
Chakrata Road
Rampur, Dehradun
248197, Uttarakhand, India

Second Donation of Two Million Chloroquine Phosphate Tablets (Amended EUA)

API Facility:
IPCA Laboratories Limited (CGMP requirements were waived)
89A–B/90/91
Industrial Estate
PoloGround, Indore—452003
India

Finished Drug Product Facility:
Bayer Pakistan Private Limited (CGMP requirements were waived)
C–21, S.I.T.E. Area, Karachi—75700
Karachi, Pakistan

Bayer donated 3 million tablets of chloroquine phosphate. For the first million tablets, the API and product were manufactured at IPCA facilities in India. The API manufacturer has not been inspected by FDA. IPCA's facilities have had various compliance actions taken against them. All known IPCA facilities previously inspected by FDA are Official Action Indicated (OAI) and on import alert.

For the additional 2 million tablets donated, the API was manufactured at the same IPCA facility in India as for the first donation, while the finished drug product was produced at a Bayer facility in Pakistan. Neither facility had been inspected by FDA. As FDA has limited information regarding the facility that manufactured the API, it is presumed that it may also have a similar or worse compliance profile. The agency did not have information from another regulatory agency regarding the CGMP status of the Bayer, Pakistan facility.

Given the lack of an approved application and any inspection history, FDA conducted tests on samples of the donated chloroquine phosphate tablets to help determine their level of quality. The product passed compendial testing requirements. In addition, FDA reviewed facility and manufacturing information provided by the manufacturers. All samples met specifications for compendial testing including identity, assay, organic impurities, dissolution, residual solvents, and heavy metal analysis. Unknown impurities were identified as ester flavorants in the samples. The ester compounds were subsequently identified as being associated with fruit flavoring (banana), in quantities consistent with low-level contamination. Additional screening of the tablets was conducted using LC–MS and no indication of any gross contamination was seen. As such, FDA permitted import of Bayer's donated chloroquine phosphate tablets into the United States.

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[10] *https://www.fda.gov/media/136534/download.*
[11] *https://www.accessdata.fda.gov/cms_ia/importalert_189.html*

We note that none of the chloroquine phosphate donated was ever distributed from the SNS for use under the EUA.

Question. Please provide all memos and other decision documents that support the issuance of the EUA, and the need for GMP to be waived.

Please provide all memos and other decision documents that support the removal of hydroxychloroquine sulfate and chloroquine phosphate manufactured by IPCA Laboratories Ltd. from the Import Alert list.

Answer. The import alert has not been lifted for any of the IPCA FDA-registered facilities. Prior to "carving out" these drugs from an import alert, FDA put in place controls for the chloroquine phosphate API and hydroxychloroquine sulfate API and tablets from IPCA facilities.

When FDA implements a "carve-out" to an import alert, FDA stipulates additional controls to balance any particular concerns. The following conditions were established of IPCA:

- Independent third-party certification of all batches prior to release from site or within 90 days of being released by IPCA's Quality Unit; FDA must be immediately notified if the third-party review identified any quality defect or data integrity breach.
- None of the batches should involve an OOS result/failure or breach of data integrity.
- Each batch must be tested in triplicate and meet the appropriate quality standards prior to its release for distribution.

Separate from the donations to the SNS, there was an existing carve-out for chloroquine phosphate API. Also separate from the donations to the SNS, FDA subsequently carved out hydroxychloroquine sulfate API and hydroxychloroquine sulfate tablets manufactured by IPCA to try to help resolve a potential shortage. Hydroxychloroquine sulfate tablets and chloroquine phosphate tablets were added to FDA's drug shortage list on March 31, 2020. The shortage of chloroquine phosphate tablets was resolved May 8, 2020. Consequently, the carve-out for chloroquine phosphate was removed on June 22, 2020. The shortage of hydroxychloroquine sulfate API and tablets resolved on June 26, 2020. The carve-out for hydroxychloroquine sulfate API and tablets was therefore removed on June 30, 2020.

On March 28, 2020, FDA issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine and chloroquine products donated to the Strategic National Stockpile (SNS) to be distributed and used for certain hospitalized patients with COVID–19. These drugs were authorized to be distributed as appropriate from the SNS to States for doctors to prescribe to certain adolescent and adult patients hospitalized with COVID–19, as appropriate, when a clinical trial was not available or feasible. The EUA required that fact sheets with important information about using chloroquine and hydroxychloroquine in treating COVID–19 be made available to health care providers and patients, including the known risks and drug interactions. The EUA also had mandatory reporting on adverse events.

The March 2020 EUA was reserved for emergency use only and is not the same as an FDA approval or licensure. At the time the EUA was issued, the drugs were shown in the lab to prevent growth of the virus that causes COVID–19 and there were reports of patients who received these drugs and improved. Because of the possibility that chloroquine and hydroxychloroquine might have helped very sick COVID–19 patients, FDA permitted the drugs to be provided only to certain hospitalized patients under the EUA who were unable to be enrolled in clinical trials. However, as noted in the authorization letter, clinical trial data results, and any information derived from clinical trials, as well as clinical trial results from studies of other investigational medical products to treat COVID–19, would continue to inform the appropriateness of the EUA.

The Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services originally requested the EUA covering chloroquine and hydroxychloroquine, and FDA granted the EUA on March 28, 2020, based on the science and data available at the time. FDA revoked this EUA on June 15, 2020, when it determined that the legal criteria for issuing an EUA were no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, including new clinical trial data, FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID–19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse

events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use. Therefore, the statutory standard for issuance of an EUA was no longer met. On June 15, in consultation with FDA, BARDA sent a letter to FDA requesting revocation of the EUA based on up-to-date science and data. A copy of the letter, FDA's letter revoking the EUA, and a memorandum outlining the scientific rationale for this decision can be found on the FDA website.

Question. On April 3, 2020, the FDA issued an EUA for N-95 respirators which included an Appendix A identifying foreign manufacturers authorized to export these devices to the U.S. On May 7, 2020, the FDA amended the EUA and removed several manufacturers from Appendix A.[12] At the time of the modification, millions of dollars' worth of these previously authorized devices had already been imported into the U.S.

Please provide all memos and other decision documents that supported the issuance of the April 3, 2020 EUA and the appendix.

Please provide all memos and other decision documents that supported the May 7, 2020 amendment the EUA, and the appendix.

Answer. The Food and Drug Administration (FDA) has used its authority to help increase the availability of personal protective equipment (PPE), including respirators, while helping to ensure patients and health care workers on the front lines can depend upon these products to protect them. One way in which FDA has helped to increase the supply of PPE in the United States is by issuing multiple emergency use authorizations (EUAs) for filtering facepiece respirators (FFRs), surgical masks, face shields, and associated decontamination systems when we determine that the statutory standard has been met. FDA has continued to evaluate these EUAs and has revised them when appropriate based on the available information to meet the changing needs of the public health emergency and to help ensure that patients and health-care providers have access to the PPE they need.

In terms of the EUA in question, FDA issued the EUA for Non-NIOSH-Approved Disposable Filtering Facepiece Respirators (FFRs) manufactured in China on April 3, 2020 to authorize the emergency use of certain FFRs for use by health-care personnel in health-care settings in accordance with CDC recommendations during FFR shortages caused by COVID–19. Respirator models were authorized by the April 3, 2020 EUA when they were shown to meet the eligibility criteria which included respirator particular product standards used in other countries that are similar to the standard NIOSH uses for NIOSH-approved N95 respirators.

FDA first issued an EUA in March to CDC–NIOSH for authorization of NIOSH approved respirators that appeared in NIOSH's CEL list. FDA also issued an EUA for "Imported non-NIOSH-approved disposable FFRs" based on respirator standards used in other countries that are similar to the standard used for NIOSH-approved N95 respirators but excluded respirator models manufactured in China from this second EUA at the time because FDA was concerned about substandard respirators manufactured in China being imported into the U.S. However, as respirator shortage concerns for healthcare personnel worsened, FDA sought additional mitigations to increase availability of respirators. One of those actions included issuing a third FFR-related EUA in April, 2020, the scope of which was limited to respirators manufactured in China, with narrow parameters (also referred to as eligibility criteria). FDA has revised these parameters and reissued this EUA as appropriate based on new information that showed, among other things, that unscrupulous actors had been using the dire need for PPE to take advantage of the unprecedented pandemic. For transparency, FDA has maintained a list of respirator models on its website that FDA has confirmed meet the eligibility criteria and that are authorized by this EUA: *https://www.fda.gov/media/136664/download.*

FDA's activities in connection with this EUA demonstrate FDA's vigilance in adapting to changing circumstances to help ensure quality products are available for health-care providers. Among other things, FDA's reissuances of this EUA have been based on new information collected as a result of FDA's increased screening of imported respirators and coordination with CDC/NIOSH to test certain lots of imported respirators. A summary of the reissuances of this EUA follows:

- On May 7, 2020, FDA revised and reissued this EUA in response to new information from CDC/NIOSH as follows:

[12] *https://www.fda.gov/medical-devices/letters-health-care-providers/certain-filtering-facepiece-respirators-china-may-not-provide-adequate-respiratory-protection-letter.*

- Revised the eligibility criterion that authorized respirator models based on performance to standards documented by independent laboratory testing. As a result of this revision, some respirator models were no longer within the scope of the authorization and so were accordingly removed from Appendix A.
- Revised the scope to add a third eligibility criterion that authorized respirator models previously listed in Appendix A under the April 3, 2020 letter of authorization if:
  - The respirator model was tested by NIOSH within 45 calendar days of the EUA issuance; and
  - Testing results indicated a minimum and maximum filtration efficiency greater than or equal to 95 percent.
- Removed the ability of importers to request addition of respirator models to Appendix A of the EUA and added a requirement directing manufacturers to provide a list of authorized importers to FDA; and
- Added recognition of the Chinese National Medical Products Administration (NMPA) registration certification that can be verified by the FDA as an eligibility criterion to the scope of authorization.
- As explained in the reissued May 7, 2020, Letter of Authorization, manufacturers who had respirators that were no longer authorized had up to 45 days to have their respirators tested by NIOSH per the revised third criterion. FDA and NIOSH tested respirators from already-imported lots of respirators or once they arrived at a U.S. port of entry. Final test results are posted on the NIOSH website,[13] Respirator Assessments to Support the COVID–19 Response.

- On June 6, 2020, FDA again revised and reissued the EUA based on the available information at the time to change the Scope of Authorization by revising the eligibility criteria to narrow the jurisdictions under which respirator models would be authorized and to provide that authorized respirators under this EUA will would no longer be authorized if they had been decontaminated.
- On October 15, 2020, FDA again reissued the EUA. Under the June 6, 2020 version of this EUA, a respirator was authorized if it met any of three predetermined eligibility criteria. Effective October 15, 2020, the EUA no longer includes the three eligibility criteria, meaning FDA will no longer review requests nor add to the list of authorized respirators—known as Appendix A—of this EUA based on those criteria. Specifically, FDA reissued the EUA to revise the Scope of Authorization to authorize only those respirators listed in the EUA's Appendix A as of the date of this reissuance. This reissuance was prompted, in part, by a respirator shortage assessment conducted by FDA to understand current product availability for both NIOSH-approved N95s and KN95 respirators and use practices for each. The assessment showed that the KN95 respirator models authorized by this EUA meet the demand for these respirators. As part of this assessment, the agency heard directly from health-care personnel that the KN95 design has limited adoption in health-care settings; from distributors that imported, non-NIOSH-approved product from China is sitting in warehouses unused; and from manufacturers that NIOSH-approved N95 production is increasing. Additionally, CDC/NIOSH continues to issue more N95 approvals.

As a result of this EUA's latest reissuance, FDA expects that staff and agency resources that were devoted to reviewing submissions to be added to Appendix A under the June 6, 2020 EUA's eligibility criteria can instead focus on other critical needs during the COVID–19 public health emergency, including continuing to work with CDC/NIOSH to help facilitate the availability of respiratory protection that meets the applicable standards and demands of health-care personnel.

FDA continues to evaluate EUAs and its policies for medical products during the pandemic and will make additional updates as appropriate to meet the needs of patients and our health care workers on the front lines of the United States response. If the committee would like more information on the FDA EUA for Non-NIOSH Approved Disposable Filtering Facepiece Respirators Manufactured in China, the agency would be happy to discuss a follow-up briefing.

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[13] *https://www.cdc.gov/niosh/npptl/respirators/testing/default.html.*

Question. The Government Accountability Office has noted the FDA's history of issuing exceptions that may allow poor quality drugs to be imported into the United States. Please provide lists of the following:

All instances since October 1, 2015 when the FDA downgraded a field inspector's recommended Official Action Indicated.

Answer. The data included in this response are limited to foreign inspections to ensure the data reflects the intent of the question as posed by the opening paragraph's mention of imported drugs. A downgrade is defined as an initial ORA recommendation of OAI and a final classification of VAI or NAI.

Fiscal Year	Concur	Downgrade	Total
2014	40 (43%)	52 (57%)	92
2015	36 (45%)	44 (55%)	80
2016	75 (51%)	73 (49%)	148
2017	83 (70%)	35 (30%)	118
2018	106 (69%)	47 (31%)	153
2019	69 (71%)	28 (29%)	97

Question. All instances since October 1, 2015 when the FDA has allowed imports from a facility that has received an Official Action Indicated finding.

Answer. If a foreign facility is found to have quality problems serious enough for FDA to classify it as OAI, the agency can place a facility on Import Alert, which is used to prevent potentially violative drugs from the facility from legally entering the United States. As part of the OAI evaluation process, FDA considers if any drug shortages could occur or if any existing shortages could be exacerbated as a result of potential compliance actions. If needed, FDA will consider Import Alert product carve-outs to alleviate potential or existing drug shortages. When FDA implements a product carve-out to an Import Alert, FDA stipulates additional controls to balance any particular concerns with importing such products. Generally, FDA will remove a facility from a CGMP-related Import Alert after an onsite re-inspection demonstrates that the problems have been remediated and the firm is in compliance with CGMP.

Question. All instances when the FDA has allowed a facility under Import Alert to import drugs into the United States.

Answer. From FY2016 through FY2019, CDER issued 74 Import Alert product carve-outs associated with 14 facilities. These products include drug products, active ingredients, and starting materials. Of the 14 facilities with Import Alert product carveouts, nine facilities imported drugs to the United States when the carveout was active. In this same time period, CDER removed 63 product Import Alert carveouts associated with seven facilities.

QUESTIONS SUBMITTED BY HON. BENJAMIN L. CARDIN

COVID–19-RELATED DRUG SHORTAGES

Question. Prescription drug shortages have been a persistent and troubling occurrence, with at least 200 drugs currently in shortage. In February, I wrote to FDA Commissioner Hahn on the issue of drug shortages related to the COVID–19 pandemic. I was concerned then that COVID–19 would worsen domestic drug shortages.

We have also seen new drug shortages tied directly to COVID–19. Hospitals have struggled to secure an adequate supply of drugs for intubating COVID–19 patients who require ventilators as well as common antibiotics and other drugs used for general surgery.

How is the FDA planning to ensure commonly used, multi-purpose drugs that are currently in COVID–19 clinical trials, are still available for people who rely on these medications? For example, the antibiotic azithromycin is being reported as in shortage by Maryland's hospitals and the FDA.

Some of the critical medications identified by Maryland's hospitals have been identified by the FDA as being in shortage for over a month. As more States begin to re-open and hospitals resume non-emergent procedures, what is the FDA's plan for supporting the supply chain, especially for medications used in general surgery and mechanical ventilation?

Given the increasing cases of Multi-inflammatory Syndrome in children, how is the FDA planning to ensure certain medications used for pediatric mechanical ventilation and the treatment of these patients, are in sufficient supply?

Answer. When FDA identifies potential shortages or supply disruptions of medical products, we use all available tools to help prevent the shortage when we can, to mitigate the impact on U.S. patients and health-care professionals, and to share information with them.

We work closely with manufacturers to make sure that, to the extent required by section 506C of the FD&C Act, they notify FDA, as early as possible, of a permanent discontinuance or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply in the U.S. This communication and the full cooperation of companies providing specific and necessary information is imperative for us to have an accurate understanding of the supply landscape and work to take proactive steps to prevent and mitigate shortages. To help human drug manufacturers submit timely and informative notifications, the agency published a guidance [14] in March about these notifications, the timelines manufacturers should follow when notifying FDA, and the details they should provide about the discontinuance or interruption of manufacturing.

In addition to the requirement that certain manufacturers submit timely notification of discontinuances and interruptions in manufacturing, we have asked manufacturers to evaluate their entire supply chain, including active pharmaceutical ingredients, finished dosage forms, and any components that may be impacted in any area of the supply chain due to the COVID–19 outbreak.

COVID–19 has led to an increased population with critical illness, necessitating sedation drug products for mechanically ventilated patients. As a result, there is a shortage of FDA-approved propofol available for use in mechanically ventilated critically ill patients, as well as shortages of alternative FDA-approved drugs like dexmedetomidine, which is approved for sedation of mechanically ventilated patients in the ICU setting. On May 8th, FDA issued an Emergency Use Authorization (EUA) for emergency use of the Fresenius Propoven 2 percent Emulsion to maintain sedation via continuous infusion in patients older than 16 who require mechanical ventilation in an ICU during the COVID–19 public health emergency. This was because, based on the totality of scientific evidence available, FDA concluded that it is reasonable to believe that the Fresenius Propoven 2 percent Emulsion may be effective to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID–19 who require mechanical ventilation in an ICU setting.

Additionally, FDA has issued guidances setting forth: (1) a temporary policy for outsourcing facilities to compound certain human drugs for hospitalized patients when hospitals experience difficulties accessing certain drugs to treat patients with COVID–19 and (2) temporary limited flexibility for State-licensed pharmacies (including hospital pharmacies), Federal facilities and outsourcing facilities that repackage or combine FDA-approved propofol products for hospitals that are having difficulty obtaining adequate supplies of the FDA-approved version in the sizes they use to support or treat patients with COVID–19. In anticipation of increased demand for certain drugs, FDA has also published product-specific guidances to support generic drug development, including for azithromycin, propofol, and hydroxychloroquine, among others.

FDA prioritizes review of any newly submitted Abbreviated New Drug Applications (ANDAs) to ensure efficient allocation of limited agency resources to areas where priority review is most likely to meaningfully increase generic drug access and ensure fairness to applicants, such as was done for chloroquine phosphate and hydroxychloroquine sulfate. Where appropriate we have expedited application assessments—including supplements—to help ensure adequate drug supply for COVID–19 patients.

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[14] *https://www.fda.gov/media/136486/download.*

Finally, per the executive order issued on August 6, 2020, FDA is working to identify vulnerabilities in the supply chain for essential medicines, medical countermeasures, and critical inputs and to mitigate those vulnerabilities.

NATIONAL SECURITY SUPPLY CHAIN LESSONS

Question. Coronavirus is a wake-up call to the United States to begin to reclaim the control of our medical supply chain.

What are the key lessons we have learned from crises affecting our supply chain and how they may impact national security?

Answer. In October 2019, the FDA-led Drug Shortage Task Force published its report, "Drug Shortages: Root Causes and Potential Solutions" (updated February 2020),[15] which examines the underlying factors responsible for drug shortages and recommends enduring solutions. The report identifies economic forces behind the three root causes for drug shortages, summarized as: (1) lack of incentives to produce less profitable drugs, (2) lack of market recognition and rewards for manufacturers with mature quality management systems, and (3) logistical and regulatory challenges that make it difficult for the market to recover from a disruption.

In October 2019[16] and again in December 2019,[17] Dr. Janet Woodcock, Director, FDA Center for Drug Evaluation and Research (CDER), testified on safeguarding our pharmaceutical supply chains before the Health Subcommittee of the House Energy and Commerce Committee. Dr. Woodcock stated, "The security of the Nation's supply rests on three main factors: freedom from dependence on foreign sources of API; the resilience of our domestic manufacturing base; and the reliability of the facilities that make products for the U.S. market." The COVID–19 pandemic has highlighted the need to repatriate some manufacturing to the United States and to increase the resilience and reliability of the supply chain by adopting advanced manufacturing technology.

All domestic finished dosage form (FDF) and API establishments are required to register with FDA, and all foreign FDF and API establishments that manufacture APIs or FDFs that is imported or offered for import into the United States are also required to register. However, many foreign FDF and API establishments incorrectly interpret the establishment registration requirements to only apply to those foreign establishments that directly ship to the United States. As a result, some foreign API and FDF facilities that ship to other foreign facilities prior to the drugs reaching the United States currently do not register with FDA.

Foreign or domestic facilities producing API intermediates are not required to register with FDA. (An API intermediate is a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API.) The lack of registration of a portion of the drug supply chain leaves the agency with significant blind spots when working to predict, mitigate, and address drug shortages. Without sufficient insight into the upstream supply chain for drug products, the agency is unaware of whether an event affecting a particular country or region could potentially disrupt the U.S. drug supply and is unable to effectively conduct appropriate oversight of potential risks in the drug supply chain. This is particularly the case for non-application products (such as products marketed pursuant to an over-the-counter (OTC) monograph) because, at least with respect to products with approved applications, we have some insight into which API sources may be used by the FDF facilities.

Additionally, there are importers that appear to be registering manufacturers without their knowledge. As a result, when the agency identifies that a potentially hazardous product is on the market or at the border pending evaluation, our investigation and discussion with the importer and manufacturers are unnecessarily delayed while we work to determine the facts of the case, the responsible parties, and the most effective path to minimize harm to consumers and patients.

Another important challenge discussed in the hearings concerns our oversight of APIs and FDFs coming into the United States, including non-sterile and sterile drugs that do not require an application to be marketed, such as API for compounding, and API for OTC monograph drugs as well as FDFs of such drugs. Under

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[15] *https://www.fda.gov/media/131130/download.*

[16] *https://energycommerce.house.gov/committee-activity/hearings/hearing-on-safeguarding-pharmaceutical-supply-chains-in-a-global-economy.*

[17] *https://energycommerce.house.gov/committee-activity/hearings/hearing-on-securing-the-us-drug-supply-chain-oversight-of-fda-s-foreign.*

current law, these drugs can be distributed to the U.S. market even if FDA has not yet had an opportunity to evaluate and inspect the manufacturing facilities. This situation puts patients at risk since they may end up taking these non-application drugs before the agency can evaluate whether or not the manufacturing facility is conforming with current good manufacturing practice (CGMP) requirements. Examples of products include OTC eyewashes, hand sanitizers, and ointments. In addition, the agency does not have authority to mandate recalls for most drugs.

Question. How do we protect our supply chain from these issues?

Answer. The Drug Shortage Task Force Report, mentioned above, also recommended enduring solutions for drug shortages, including: (1) creating a shared understanding of the impact of drug shortages on patients and the contracting practices that may contribute to shortages; (2) developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities; and (3) promoting sustainable private sector contracts (*e.g.,* with payers, purchasers, and group purchasing organizations) to make sure there is a reliable supply of medically important drugs. While these recommendations are not directed specifically toward supply chain disruptions, they may serve to encourage supply redundancy and more robust supply chains.

These are long-term solutions that will require private as well as public efforts and a change in business practices. Over the shorter term, FDA has supported the development of ICH Guideline Q12: Technical Regulatory Considerations for Pharmaceutical Product Lifecycle Management, which will improve the resilience of the manufacturing base by reducing the regulatory burden on companies wishing to expand production capacity or upgrade their facilities. FDA is also developing guidances for industry on risk management plans to prevent or mitigate the risk of drug shortages and improved information sharing.

In 2014, FDA launched the Emerging Technology Program (ETP), which encourages and supports the adoption of innovative technology to modernize pharmaceutical development and manufacturing through close collaboration with industry and other stakeholders starting with early technology development.

Question. Looking ahead, how do we diversify the American health-care system's manufacturing supply chain?

Answer. As Dr. Janet Woodcock mentioned in her October 2019 testimony, adoption of advanced manufacturing technologies would support the repatriation of some of pharmaceutical manufacturing to U.S. soil. Using traditional manufacturing, the United States is at a significant disadvantage to China and India because of their lower labor, materials, transportation, and real estate costs and weaker environmental regulations. Advanced manufacturing, which is much more efficient and has a smaller environmental impact, can offset foreign countries' advantages and enable the United States to rebuild its pharmaceutical manufacturing base.

Question. How do we incentivize domestic manufacturing?

Answer. FDA continues to work with relevant stakeholders (*e.g.,* other Federal agencies and drug manufacturers) to facilitate the adoption of advanced manufacturing technologies as one of the proactive approaches to prevent drug shortages and ensure continuous supply of critical drugs in the United States. Advanced manufacturing technology, which can be more cost-effective and environmentally friendly than traditional manufacturing technology, may enable the United States to play a larger role in pharmaceutical manufacturing. These include initiatives to enhance the efficiency of drug manufacturing by utilizing technology (such as through the use of 3D printing, miniaturization, continuous manufacturing, and other techniques). By supporting education for a domestic workforce trained in these areas, skilled U.S. workers would be able to be part of this emerging trend in drug manufacturing. By moving from batch-to-batch production to continuous manufacturing, drugs can be produced much more quickly, and the quality is much more uniform. As part of the COVID–19 response, the Department has engaged companies to help promote domestic manufacturing and additional sources of medical products.

QUESTIONS SUBMITTED BY HON. ROBERT MENENDEZ

Question. The FDA's contradictory statements and actions related to hydroxychloroquine and chloroquine have sown confusion and potentially caused harm and even death among COVID–19 patients. Will the FDA be revaluating how they issue Emergency Use Authorizations (EUAs) for other potential COVID–19 treatments to

ensure the issues surrounding the EUAs for hydroxychloroquine and chloroquine are not repeated?

Answer. Under the criteria set forth in section 564 of the Federal Food, Drug, and Cosmetic Act, FDA considers the totality of scientific data available when determining whether to issue an Emergency Use Authorization (EUA). If, based on the totality of the scientific evidence available, it is reasonable to believe that the product may be effective for the specified use, FDA may authorize its emergency use, provided that other statutory criteria for issuing an EUA also are met. For example, FDA must determine whether the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product.

When FDA issued the March 28, 2020, EUA for chloroquine and hydroxychloroquine, the results of clinical trials were not yet available; however, lab data and anecdotal clinical evidence suggested that those drugs could potentially be effective in treating severe cases of COVID–19. Applying the section 564 criteria to assess the evidence available at that time, as well as to assess the known and potential benefit of the products versus the known and potential risks at that time, FDA issued the EUA.

As further required under section 564, FDA continued to review the appropriateness of the EUA as the results of clinical trials and other evidence became available. Based on this continuing review, on June 15, 2020, FDA determined that these drugs were unlikely to be effective in treating severe cases of COVID–19 and that statutory criteria for issuance were no longer met. Therefore, FDA revoked the EUA. The agency notes that during a public health emergency, EUAs are processed expeditiously to permit the availability of promising treatments. Each EUA is evaluated independently, as products and circumstances are unique to each EUA.

Question. Please describe, in detail, the FDA's decision-making process to issue an EUA for hydroxychloroquine and chloroquine on March 28, 2020, including all communications with White House officials on this topic. Additionally, please provide copies of any relevant communications.

Answer. On March 28, 2020, FDA issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine and chloroquine products donated to the Strategic National Stockpile (SNS) to be distributed and used for certain hospitalized patients with COVID–19. These drugs were authorized to be distributed from the SNS to States for doctors to prescribe to certain adolescent and adult patients hospitalized with COVID–19, as appropriate, when a clinical trial was not available or feasible. The EUA required that fact sheets with important information about using chloroquine and hydroxychloroquine in treating COVID–19 be made available to health-care providers and patients, including the known risks and drug interactions. The EUA also had mandatory reporting on adverse events.

The March 2020 EUA was reserved for emergency use only and is not the same as an FDA approval or licensure. At the time the EUA was issued, the drugs were shown in the lab to prevent growth of the virus that causes COVID–19 and there were reports of patients who received these drugs and improved. Because of the possibility that chloroquine and hydroxychloroquine might have helped very sick COVID–19 patients, FDA permitted the drugs to be provided only to certain hospitalized patients who were unable to be enrolled in clinical trials under the EUA. However, as noted in the authorization letter, clinical trial data results, and any information derived from clinical trials, as well as clinical trial results from studies of other investigational medical products to treat COVID–19, would continue to inform the appropriateness of the EUA.

The Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services originally requested the EUA covering chloroquine and hydroxychloroquine, and FDA granted the EUA on March 28, 2020, based on the science and data available at the time. FDA revoked this EUA on June 15, 2020, when it determined that the legal criteria for issuing an EUA were no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, including new clinical trial data, FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID–19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use. Therefore, the statutory standard for issuance of an EUA was no longer met. On June 15, in consultation with FDA, BARDA sent a let-

ter to FDA requesting revocation of the EUA based on up-to-date science and data. A copy of the letter, the FDA letter revoking the EUA, and a memorandum outlining the scientific rationale for this decision can be found on the FDA website.

Regarding your question about communications with the White House in the decision process for the March 28, 2020, EUA, FDA notes that its role is to make independent, science-based decisions to bring new therapies to sick patients as quickly as possible, while at the same time supporting research to further evaluate whether these therapies are safe and effective for treating patients infected with this novel virus. The March 2020 EUA authorizing the drugs' use for certain hospitalized patients with COVID–19 was prepared by expert FDA career staff and reflects internal scientific discussion.

Question. Pharmaceutical and diagnostic companies are investing in the development of products to diagnose and treat COVID–19. In an effort to assist these companies in bringing a potential vaccine to market and mitigate the spread (and subsequent deaths) from COVID–19, has the FDA relaxed or changed any of its regulations or guidance regarding human clinical trials? If so, please explain these changes and how they diverge from FDA's normal clinical trial practices.

Answer. Clinical trials are being impacted by the COVID–19 public health emergency. Challenges may arise, for example, from self-isolation, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID–19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administration or use of the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

FDA has not changed any of its regulations regarding the conduct of clinical trials during the COVID–19 pandemic. However, to address these and other challenges, FDA promptly issued guidance to assist sponsors conducting clinical trials during the COVID–19 public health emergency in meeting regulatory requirements. See FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID–19 Pandemic.[18] This guidance was issued on March 18, 2020, and then updated multiple times, most recently on September 21, 2020. Since the guidance was issued, FDA has added 25 question and answers, many in response to the over 500 inquiries to the mailbox *Clinicaltrialconduct-COVID19@fda.hhs.gov* that FDA set up with the issuance of the first guidance to assist the clinical trial community.

FDA also established the Coronavirus Treatment Acceleration Program (CTAP) to facilitate communications with sponsors developing a host of therapies to treat and prevent COVID–19. CTAP uses every available method to move new treatments to patients as quickly as possible, while maintaining our focus on determining whether they are helpful or harmful. We continue to support clinical trials that are testing new treatments for COVID–19 so that we gain valuable knowledge about their safety and effectiveness.

In CTAP, CDER and CBER scientific experts, such as virologists, allergists, pulmonologists, and critical care specialists, continue to take the lead to advise sponsors how to advance drug development programs and of course to review actual incoming submissions. These clinical review teams are supported by a new, robust administrative backbone to receive a high volume of incoming proposals and inquiries and make sure they go to the right place. Sometimes the inquiry is from someone who needs very basic regulatory advice—about the difference between NIH and FDA, for example—whereas other inquiries may be from drug developers who are well down the road with clear scientific rationales and strong evidence. We have posted additional information about these efforts, including the number of drug development programs and clinical trials reviewed by FDA for COVID–19, on the CTAP website.[19]

CTAP does not change pre-existing roles, responsibilities, or decision rights concerning drug development and approval; instead, CTAP provides much more robust support to our scientists so they can work the science in a more swift, nimble, and focused manner.

Question. The FDA has issued guidance to promote diversity in clinical trials. However, certain populations continue to be underrepresented in many clinical trials. With these challenges in mind, what recent guidance or policies has FDA in-

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[18] *http://wcms-internet.fda.gov/media/136238/download.*

[19] *https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.*

stituted to ensure diversity in clinical trials for potential COVID–19 vaccine candidates?

If any written policy or guidance has been issued, please forward that information to my office. If no new policies or guidance have been issued, please explain why, particularly in light of FDA's recognition of diversity in drug trial testing as an issue.

Answer. A significant step in spurring the development of the data needed to demonstrate the safety and efficacy of vaccines to prevent COVID–19 was the issuance of FDA's guidance, Development and Licensure of Vaccines to Prevent COVID–19.[20] The guidance document outlines FDA's expectations for the development of these vaccines, including design of clinical trials, trial populations, safety and efficacy considerations, and information needed for our assessment of manufacturing and facility information.

We are often asked about clinical trials for COVID–19 vaccines and the importance of diversity in clinical trial participants. It is critical for vaccines to work for everyone in the indicated populations. That is why FDA strongly encourages enrollment of all people—including racial and ethnic minorities, older adults, pregnant women and women of childbearing age, and, as appropriate, children—in clinical trials to test COVID–19 vaccines, as outlined in the recommendations in our guidance.

Similarly, FDA's Guidance COVID–19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry[21] states that racial and ethnic minority persons should be represented in clinical trials. Sponsors should ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minorities to recruit a diverse study population.

Question. In 2018, FDA released expectations and recommendations on the collection of racial and ethnic data to create a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA regulated medical products. Since the release of these expectations and recommendations, has FDA seen an increase in the standardized collection of racial and ethnic data? If so, please provide concrete examples of when the collection of this information has substantially influenced FDA's approval of a particular drug. If FDA has not seen an improvement of racial and ethnic data collection, please provide concrete steps the agency intends to take to improve collection and further incentivize pharmaceutical companies to collect this information.

Answer. In response to the FDA Safety and Innovation Act of 2012, FDA issued Guidance for Industry in October 2016 on the Collection of Race and Ethnicity Data in Clinical Trials. The guidance provides FDA's expectations for and recommendations on collecting and reporting race and ethnicity data in submissions for clinical trials for FDA-regulated medical products conducted in the United States and abroad. The guidance also states that FDA's expectations are that sponsors enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity.

Furthermore, the results of FDA's routine review of a medical product's safety and effectiveness by race and ethnicity can identify essential information needed for the safe and effective use of the product. For example, the labeling for ACE inhibitors, a class of antihypertensive drugs, inform prescribers that controlled trials have shown that these drugs are less effective in black patients than non-black patients. These drugs have also been associated with a higher rate of angioedema in black than in non-black patients. Another drug, BiDil (isosorbide dinitrate/hydralazine HCl), was approved for the treatment of heart failure only in self-identified black patients because there was little evidence of effect among white patients.

Question. Does the FDA have a plan to improve racial and ethnic data collection from pharmaceutical companies during clinical drug trials?

Answer. FDA is committed to encouraging diverse participation in research used to support marketing applications for regulated medical products. Following the FDA Safety and Innovation Act of 2012, specifically section 907, and the priorities set forth in FDA's Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data, the agency has continued its ongoing efforts to support di-

[20] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.*
[21] *https://www.fda.gov/media/137926/download.*

verse participation in clinical trials through hosting public meetings, developing tools, and issuing guidance documents. Over the past few decades, FDA policy initiatives have focused on promoting enrollment practices that lead to clinical trials better reflecting the population most likely to use the product if the product is approved.

FDA's Office of Minority Health and Health Equity (OMHHE) has continued to work to advance racial and ethnic minority participation in clinical trials through its Diversity in Clinical Trials Initiative, including a variety of culturally and linguistically competent strategies and resources. This includes an ongoing campaign to provide positive reinforcements and raise awareness on the need for racial and ethnic minority populations to participate in clinical trials.

Additionally, FDA issued a draft guidance to assist sponsors in enrolling and retaining a diverse clinical trial population that reflects the patient population most likely to use the drug if it is approved. See *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry* (June 2019).[22]

Question. What resources does the FDA need to ensure the United States is at the forefront of advanced manufacturing for pharmaceuticals?

Answer. FDA believes that advanced manufacturing technologies could enable U.S.-based pharmaceutical manufacturing to regain its competitiveness with foreign countries, and potentially ensure a stable supply of drugs critical to the health of U.S. patients. Advanced manufacturing offers many advantages over traditional pharmaceutical manufacturing, and if the United States invests in this technology, it can be used to reduce the Nation's dependence on foreign sources of APIs, increase the resilience of our domestic manufacturing base, and reduce quality issues that trigger drug shortages or recalls.

In FY 2020, FDA's Center for Drug Evaluation and Research received $9M of one-time supplemental funding which will be used to continue to modernize and enhance science in areas related to advanced pharmaceutical manufacturing. Knowledge generated from these activities, together with the information provided by sponsors or applicants, can help enable science- and risk-based assessment, inspection and surveillance, establish best practices, support standard, policy and guidance development, and provide important training on novel manufacturing technologies.

Although the success to date demonstrates that the adoption of advanced manufacturing technology allows for domestic manufacturers to be competitive in the market place, the limited number of approved applications demonstrates there are still barriers to entry beyond the regulatory barriers the Emerging Technology Program is designed to reduce. Therefore, it is important for other incentives to be made available to address the non-regulatory barriers to the adoption of advanced manufacturing. However, FDA does not have significant expertise in determining what incentives might be effective in spurring industry adoption of new technology.

QUESTIONS SUBMITTED BY HON. SHERROD BROWN

DIVERSIFIED SUPPLY CHAIN

Question. How important is it for the U.S. to diversify sources for APIs and finished drug products?

Answer. FDA understands the significant impact of the drug supply chain on patient care. Redundancy and geographic diversity are important keys to ensuring a robust drug supply chain. A drug supply chain that has multiple establishments in different geographic regions is a more resilient supply chain. A supply chain is even more resilient if there are multiple, geographically diverse sources of active pharmaceutical ingredients (APIs). The resiliency lies in the fact that if a natural disaster or disease outbreak affects establishments or suppliers in one geographic region, or one of the suppliers leaves the market, there are other establishments not affected by the disruption that can still supply the market.

Question. Does the FDA have any strategies or policies in place to ensure the U.S. does not rely on a single source for any APIs or finished drug products?

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[22] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial*.

Answer. FDA cannot prevent manufacturing concentration or require redundancy of manufacturing capability and capacity. Nor can FDA require a company to manufacture a drug, maintain a certain level of inventory of drug product, or reverse a business decision to cease manufacturing.

However, the Coronavirus Aid, Relief, and Economic Security Act (the CARES Act) amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to require that manufacturers develop, maintain, and implement, as appropriate, a redundancy risk management plan for certain drugs, APIs, and associated devices. FDA staff are working to issue guidance for industry to provide manufacturers with information concerning this new requirement.

Question. What are some ways Congress could facilitate the diversification of sources for APIs and finished drug products, particularly for more essential medicines?

Answer. As noted above, FDA cannot prevent manufacturing concentration or require redundancy of manufacturing capability and capacity. Nor can FDA require a company to manufacture a drug, maintain a certain level of inventory of drug product, or reverse a business decision to cease manufacturing.

The lack of more comprehensive pharmaceutical reporting limits FDA's insights into the supply chain, including FDA's ability to assess critical infrastructure as well as manufacturing quality and capacity for pharmaceuticals. FDA does not currently receive detailed manufacturing volume information on a quarterly basis from either human or animal drug manufacturers.

The adoption of advanced manufacturing could enable U.S.-based pharmaceutical manufacturing to regain its competitiveness with China and other foreign countries, and potentially ensure a stable supply of drugs critical to the health of U.S. patients. Advanced manufacturing technology, which FDA supports through, among other things, its Emerging Technology Program (ETP), has a smaller facility footprint, lower environmental impact, and more efficient use of human resources than traditional manufacturing.

MANDATORY RECALL

Question. Does FDA agree that mandatory recall authority could help expedite the FDA's recall process and get potentially harmful drugs off the market faster, even when a pharmaceutical company would otherwise comply with a voluntary recall request?

Answer. The main benefit of mandatory drug recall authority is that it would expedite the initiation of a recall and get potentially harmful drugs off the market when a drug company either refuses or is reluctant to comply with a voluntary recall request. In addition, although FDA generally prefers not to require a recall when a company is otherwise willing to comply with a voluntary recall request, there can be circumstances where the potential for FDA to require a recall may allow FDA and a drug company to reach an agreement on the scope of a recall faster.

When companies undertake recalls, they are an effective method of removing defective FDA-regulated products that have been distributed commercially, particularly when those products present a danger to health. Recall actions are conducted by manufacturers and distributors to protect the public health from products that present a risk of injury. A recall may be undertaken voluntarily at any time by manufacturers and distributors, or initiated at the request of FDA. FDA generally directs a recall request to the firm that has primary responsibility for the manufacture and marketing of the product. The Agency works with manufacturers and distributors to develop a recall strategy and to publicize information to the public. FDA also monitors the effectiveness of any recall and takes additional actions as appropriate.

Consumers can be exposed to risks for extended periods of time when firms refuse to or delay the recall of defective or harmful drugs. Below we provide examples of hand sanitizers, homeopathic teething tablets and gels, and other non-application products where mandatory recall authority would have been helpful to our efforts to remove dangerous products from the market expediently.

During the COVID–19 pandemic, FDA determined that some hand sanitizer products distributed or offered for import in the United States, particularly those manufactured in Mexico, were contaminated (*e.g.,* contained methanol) and/or subpotent. Methanol is poisonous and can cause adverse events, such as dizziness, blindness,

and death. In these cases the methanol-contaminated hand sanitizer led to the deaths of U.S. consumers. FDA quickly reached out to manufacturers to recall these dangerous drugs. Some of the manufacturers cooperated, but many did not. Some examples include:

Delayed Recalls of Hand Sanitizers

- Eskbiochem was contacted by FDA on June 17, 2020, to recommend the company recall its hand sanitizer products from the market due to the risks associated with methanol poisoning. The company took no action and actually requested its detained product be sent back so the firm could distribute it to the domestic Mexican market. Some, but not all product, was eventually recalled 5 weeks later by distributors. (96,613 liters of hand sanitizer were distributed and distributors were able to recall 36,886 liters; see: *https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-consumers-not-use-hand-sanitizer-products-manufactured-eskbiochem).*
- Soluciones Cosmeticas was contacted by FDA on July 1, 2020, to recommend recall of adulterated hand sanitizer but was reluctant to recall. Only after additional communication in which FDA notified the firm that a State department of health had reported cases of death linked to the use of their product did the firm agree on July 10, 2020, to voluntarily recall 3.3 million liters of hand sanitizer. (See: *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/soluciones-cosmeticas-sa-de-cv-609057-08042020.*)

Refusals to Recall Hand Sanitizers

- Since June 2020, there have been more than five manufacturers who have refused to recall their subpotent (including lack of active ingredient) and/or methanol contaminated hand sanitizer. These manufacturers had produced over 206,766 liters of adulterated hand sanitizer. The following warning letters provide more information on recent incidents relating to hand sanitizers where mandatory recall authority would have aided our efforts:

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/quimica-magna-de-mexico-sa-de-cv-608751-10152020.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/grupo-insoma-sapi-de-cv-608768-10232020.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/real-clean-distribuciones-sa-de-cv-608900-10272020.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/asiaticon-sa-de-cv-609162-10292020.

- In January 2017, FDA contacted a manufacturer of homeopathic infant teething tablets to convey serious concerns about the inconsistent amounts of belladonna alkaloids (also known as deadly nightshade) contained in the tablets sometimes far exceeding the amount claimed on the label. Belladonna alkaloids have anticholinergic effects, including disorientation, hallucinations, fast heart rate, and may also cause drowsiness in infants. (See: *https://www.fda.gov/news-events/press-announcements/fda-confirms-elevated-levels-belladonna-certain-homeopathic-teething-products.*)
- After FDA contacted the firm with these serious concerns, the firm sent a letter stating it declined to take action on those products, further stating its belief "that the public is amply protected." FDA subsequently sent a Requested Recall letter signed by the Associate Commissioner of Regulatory Affairs to the firm, which announced a recall almost four months after FDA had initially contacted the firm. (See: *https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-standard-homeopathic-companys-nationwide-voluntary-recall-hylands-teething-tablets.*)
- In August 2020, FDA twice contacted a repacker of goldenseal root powder to discuss laboratory findings of high counts of various bacteria, including multiple pathogens in its product and to request a voluntary recall. The product was distributed nationwide and purchased between the dates of January 25, 2015, and August 4, 2020. Because the firm failed to take action, FDA issued a press release warning the public about use of the contaminated product, which could lead to serious infections and death in infants and individuals with weak immune systems. The firm had received a report from FDA of one infant death associated with use of this product on the umbilical cord

stump. The firm initiated a voluntary recall three days after FDA issued the press release.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-consumers-not-use-goldenseal-root-powder-distributed-maison-terre.

https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/maison-terre-issues-voluntary-nationwide-recall-organic-goldenseal-root-powder-due-microbial.

- In June 2016, FDA alerted both the own-label distributor and the contract manufacturer of a potentially contaminated Diocto docusate (oral liquid docusate sodium) product, and the firms agreed to quarantine the product. The product was suspected as a link to a *Burkholderia cepacia* outbreak of pediatric ICU patients in five states. Use of these contaminated products in patients whose immune system is compromised could result in infections, which may be life-threatening. In July 2016, FDA laboratory testing revealed the contamination of Diocto docusate with *B. cepacia,* demonstrating a direct link between the drug and the outbreak. The investigation also detected *B. cepacia* in the water system used to manufacture the product. Days later, the contract manufacturer agreed to recall the Diocto docusate product; three weeks later, it agreed to recall all of its liquid drug products.
- In July 2017, a second outbreak of *B. cepacia* in oral liquid docusate sodium products occurred. The contract manufacturer was uncooperative and FDA extended communication to distributors. While a voluntary recall was eventually initiated by the five distributors, the contract manufacturer's lack of cooperation delayed the recall and lengthened the exposure of hospital patients to the contaminated product.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-multistate-outbreak-burkholderia-cepacia-infections.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-2017-burkholderia-cepacia-contamination.

These are some examples involving serious risks where firms delayed recall of harmful products putting consumers and patients at risk. If the Agency had mandatory recall authority, the Agency could have facilitated removal of the drugs from the market months earlier, reducing the time that consumers, including infants, were potentially exposed to harmful drugs.

API REPORTING/INSPECTIONS

Question. Does FDA know what percent of API is produced in the U.S.? Not the facilities manufacturing, but the percent of actual API product that comes from the U.S. versus other countries?

Answer. No. As noted above, the lack of comprehensive pharmaceutical reporting limits FDA's insights into the supply chain. Although FDA can describe the locations of API manufacturing facilities, we cannot determine the volume of API produced in a given location. For a detailed walkthrough of the limitations of FDA's data, please see Dr. Janet Woodcock's testimony before the House Energy and Commerce Committee's Subcommittee on Health at an October 2019 hearing available here: *https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019.*

Question. Does FDA know what percent of chemical materials used to manufacture API are produced in the U.S. versus other countries?

Answer. No; see responses to questions above.

Question. Does the FDA know what percent of FDF of human drugs is produced in the U.S.?

Answer. No; see responses to questions above.

Question. What more could and should the FDA do to collect additional information on API and its manufacturing and distribution under current law?

Answer. The CARES Act amended section 510(j) of the FD&C Act to require "Each person who registers with the Secretary under this section with regard to a drug shall report annually to the Secretary on the amount of each drug listed under paragraph (1) that was manufactured, prepared, propagated, compounded, or processed by such person for commercial distribution . . ." which when implemented,

will give the agency information about how much and which APIs are manufactured at different facilities.

Question. What additional authorities could Congress provide the FDA that would be helpful in collecting additional information on the manufacturing and distribution of API?

Answer. The agency still needs information to better connect the API and FDF manufacturers as noted in the responses to questions three and five. It would also be helpful for FDA to be better able to obtain information about the API intermediates used to manufacture the API.

Question. What would it take to initiate a strategic API reserve, as discussed by Senator Cassidy during the June 2020 Senate Finance Committee hearing?

Answer. The agency understands the significant impact of the drug supply chain on patient care and does everything within its authority to help prevent interruptions in the supply chain. Taking steps to ensure patients have an adequate supply of critical drugs is an important endeavor. However, care must be taken with respect to any effort to shore up the supply chain so as not to create new, unintended risks to the supply chain. The major risks with creating a stockpile or reserve of specific medicines are that the announcement of the creation of the stockpile could cause a supply disruption by diverting production toward particular ingredients and products and it could cause others to seek to create their own stockpile.

Question. What additional information related to the drug supply chain would be helpful for FDA to have, but that the agency doesn't currently have the authority to collect?

Answer. See responses to questions above.

TESTING

Question. What percent of drugs does the FDA currently test for established quality specifications?

Answer. Pharmaceutical manufacturers, no matter where they are located, are responsible for ensuring that quality products reach U.S. patients. Manufacturers are required to test drug materials and final APIs and final drug products to verify they conform with existing standards before distribution. FDA's role is to provide sufficient oversight to help ensure that companies fulfill their responsibilities and to take appropriate action when they do not. This oversight includes testing selected finished drug products and the APIs used to make these products after they are on the market. See our response to the question below for more information on our risk-based approach to quality testing.

Question. Has the FDA ever required a pharmaceutical manufacturer to provide proof of batch testing or test results for established quality specifications postmarket?

Answer. Current regulations require drug product manufacturers to test representative samples of all components (ingredients) from each lot of each shipment before use in manufacturing the drug product. Drug product manufacturers are required to test representative samples of each lot of finished drug product to verify it meets specifications before releasing the lot to market. Testing requirements also include testing during the processing of APIs and final products to confirm quality after significant stages of production. Generally during current good manufacturing practice (CGMP) inspections, we review the records that manufacturers must maintain regarding required testing, including testing for known impurities and degradation compounds, and we evaluate the implementation of other manufacturing controls and practices designed to prevent unexpected and objectionable impurities in a drug.

The FDA has the authority to conduct examinations and/or sample collections to determine if the product offered for import is in compliance with the FDA regulations and laws. As part of the entry review process, the FDA entry reviewers designate entries for examination. This examination may consist of any combination of a field examination, label examination, and/or sample collection. For example, for importation of heparin, FDA routinely reviews test results and other data accompanying the importation entry on a case-by-case basis. FDA also tests samples to verify purity.

Question. Is it accurate to say that the FDA is unable to identify the full range of drugs that fail to meet the established quality specifications as a result of its limited testing capacity?

Answer. FDA has a longstanding program to regularly sample and test marketed drugs and APIs for conformance to specifications. We select hundreds of samples each year based on certain criteria.

- Some testing decisions are event-driven. For example, we might test product samples after receiving a pattern of complaints about adverse events, quality issues, or reduced effectiveness. These reports come to FDA through consumer complaints, field alert reports, and MedWatch: The FDA Safety Information and Adverse Event Reporting Program.
- We also rely on the experience of internal and external experts to alert us to emerging safety, effectiveness, or quality issues with currently marketed drug products. For example, results from independent research may require FDA testing and investigation.

Sometimes, manufacturing or facility concerns may trigger additional FDA monitoring and testing. For instance, FDA may sample products with difficult manufacturing processes or drug products with complex dosage forms such as patches, drugs designed to target a specific area, and drugs that release the active ingredient in a controlled manner.

FDA may also sample drugs produced by manufacturing processes that require additional controls to ensure each dosage unit will perform as expected, such as delivering a precise amount of active ingredient within a narrower range, because even slight deviations could cause quality issues.

We use a risk-based approach to quality testing. This means that in cases where there is a known or likely safety, effectiveness, or quality issue with a product, FDA scientists perform tests specifically for this vulnerability. For example, if an API is likely to become contaminated with a harmful impurity during the manufacturing process, FDA tests for that specific impurity, rather than testing for all potential impurities. Additional reasons products may warrant testing under FDA's testing program include: products that are the most used drugs (including prescription brand-name and generic drugs); drugs considered critical to countering terrorism attacks; and newly approved or first-time generic prescription drugs.

Through our risk-based import screening tool, PREDICT (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting), FDA focuses agency import resources, including activities such as examinations and sample collections, on higher-risk products being offered for entry into U.S. commerce. PREDICT uses automated data mining, pattern discovery, and automated queries of FDA databases to determine the potential risk of a shipment. The analytics tool takes into consideration the inherent risk of a product and information about the previous history of importers, manufacturers, and shippers. As part of our COVID–19 response, FDA has adjusted PREDICT screening to account for firms whose foreign inspection was postponed due to COVID–19 travel restrictions.

FDA labs acquire samples for testing by a number of different mechanisms, including directly from consumers and purchases from the U.S. market via distributors, wholesalers, and retail pharmacies. FDA has found that approximately 1 percent of samples tested, both foreign and domestic, fail to meet quality standards. In addition, FDA investigators can collect the samples directly at drug manufacturing sites and deliver or send them to FDA testing labs (maintaining chain of custody). If required, FDA also has the ability to purchase samples online while retaining anonymity. Finally, some samples are sent to FDA labs directly from manufacturers as the result of information request (IR) letters from FDA assessor staff. In many cases, such samples are requested to verify test results on the same batches the firms supply to FDA. Using this "trust but verify" approach, the agency can use the most accurate available data to make regulatory decisions.

Question. If the FDA and its third-party partners batch-tested all of the drugs on the market, do you expect the percent of drugs that fail to meet the established quality specifications would be greater than 1 percent, and closer to that of Valisure's 10 percent?

Answer. The agency itself does not have the ability to test samples from every batch of all drug APIs and drug products on the market. No lab has that capacity. Millions of drug product batches are sold in the U.S. every year, which can amount to trillions of individual tablets, capsules, and other dosage forms. Approximately

800,000 different lots of API and/or drug product are imported each year. FDA instead utilizes a risk-based approach to quality testing as described above and oversees compliance to the required testing performed by each manufacturer. FDA also works with other national drug regulatory agencies to leverage resources and testing done outside the U.S., which can help inform testing priorities of the U.S. drug supply. If the findings of third-party laboratory testing alert FDA to a quality issue, FDA may investigate.

The agency has greater confidence in the reliability of its own testing methods and results. Testing methods developed by FDA are validated and the results are repeatable.

Sound science is critical for effective action, and even well-intentioned testing should be confirmed for accuracy before alerting the public or taking action. FDA has posted testing methods on the FDA website for industry, third-party laboratories, and international regulators. We welcome others to use them or to ensure they use similarly sound and validated methods.

Manufacturers may choose to use an independent third party to perform certain tests if, for example, they have reason to be concerned about the reliability of their own results or to access sophisticated methods or equipment that may not otherwise be available to them. However, FDA does not believe that independent chemical batch-level testing and verification of the chemical content of all pharmaceuticals is necessary or feasible. As a general principle, the degree of regulatory scrutiny over batch-level testing should be commensurate with the degree of risk, and an independent tester cannot evaluate the risk without sufficient knowledge of all manufacturing processes. Additionally, testing methods can only be developed with a target analyte in mind; testing of all possible chemical impurities or contaminants is not feasible. Beyond the problem of the volume of potential impurities to test, an independent third party would need information concerning the formulation and manufacturing of a product to determine which chemical tests are appropriate and to develop suitable methods for detection of impurities.

As part of FDA's risk-based approach, the agency does take complaints or third-party laboratory results into account when deciding which drugs to analyze. However, third-party laboratories may not use standards as outlined in the USP, or follow scientifically sound procedures for validating an analytical method. Improper development and validation of analytical methods can result in inaccurate results. An example is outlined in the following manuscript, which can be accessed at *https://pubmed.ncbi.nlm.nih.gov/32613429/:*

> Yang J., Marzan T.A., Ye W., Sommers C.D., Rodriguez J.D. and Keire D.A. "A Cautionary Tale: Quantitative LC–HRMS analytical procedures for the analysis of N-Nitrosodimethylamine in metformin." *AAPS J.,* 22(4), 89– (2020).

Question. Are there additional authorities or funds that would enable the FDA or its third-party partners to test a greater percent of the drug product in U.S. commerce?

Answer. Quality cannot be tested into products. Drug manufacturers must have validated processes and methods, and follow CGMPs to ensure the quality of the drugs they are manufacturing. While CGMPs require testing by the manufacturer and FDA has a longstanding program to regularly sample and test marketed drugs and APIs, testing alone is not adequate to ensure quality. It is important that drugs are manufactured under conditions and practices required by the CGMP regulations to assure that quality is built into the design and manufacturing process at every step. Facilities that are in good condition, equipment that is properly maintained and calibrated, employees who are qualified and fully trained, and processes that are reliable and reproducible are a few examples of how CGMP requirements help to ensure the safety and efficacy of drug products.

Question. What other procedures, other than batch testing, could help ensure all drugs in U.S. commerce meet established quality specifications?

Answer. It is the responsibility of all drug manufacturers to ensure their products are of acceptable quality, that is, consistently safe, effective, and free of objectionable contamination and defects. Drug manufacturers must ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of drugs are adequate to assure and preserve identity, strength, quality, and purity. FDA continues to review the quality of drug products throughout the life cycle of the products, and may take regulatory action when the agency deter-

mines that a product in the market violates provisions of the FD&C Act or presents a danger to health.

ADDITIONAL QUESTIONS

Question. What practices/alternative tools (like sampling, using authority under 704(a)(4), etc.) do you see carrying forward past pandemic? In other words, are there practices you use now that you anticipating continuing even after the public health threat dissipates and you're able to return to more normal evaluations?

Answer. Prior to the COVID–19 pandemic, FDA had utilized alternative tools such as sampling and testing of drugs in commerce, and requesting records and other information under section 704(a)(4) of the FD&C Act. During the COVID–19 pandemic, FDA expanded the use of records requests under section 704(a)(4) to evaluate firms and regulated products to address health concerns, travel restrictions and advisories which postponed routine on-site inspections. In addition, we expanded the use of Mutual Recognition Agreements (MRAs) to include use of third country reports from capable authorities and product sampling programs. FDA has also begun to add new tools to facilitate remote interactive evaluations of firms, including live streams, teleconferences, and screen sharing. FDA expects to continue to utilize these tools as part of a comprehensive oversight approach beyond the COVID–19 pandemic and will continue to evaluate these novel tools to employ best practices in the future.

Question. The two pilot programs mentioned at the very end related to quality management maturity—what is the timeline for those programs and next steps on building that assessment system out?

Answer. FDA has formed a multidisciplinary multi-center working group to facilitate the development of the quality management maturity (QMM) rating program for drug manufacturers. A framework will be developed that is intended to objectively assess and rate the QMM of manufacturing sites using facilitated assessments along with other surveillance intelligence related to the site. In development of the framework, FDA will need to consider such things as standardized assessment tools, policies and regulations, industry incentives, transparency, and communication.

To better inform the development of a framework for objectively assessing and rating the QMM of manufacturing sites, the Office of Pharmaceutical Quality (OPQ) has contracted with two third-party vendors to conduct two pilot programs. One pilot is focused on domestic manufacturers of finished dosage form products (FDFs), and the other pilot is focused on foreign manufacturers of active pharmaceutical ingredients (APIs). Each vendor will develop a QMM assessment tool, train FDA staff on performing and scoring QMM assessments, and conduct facilitated assessments of manufacturing sites. Due to the ongoing COVID–19 pandemic, most if not all the assessments will be conducted virtually.

As an incentive for participating in these pilot programs, volunteer sites will receive QMM reports that can empower their continuous improvement programs. In addition, these participating manufacturers could benefit in the future by better understanding QMM ratings when they roll out and begin to enable health systems, other purchasers, and payers of drugs to differentiate among drug manufacturers.

Pilot participants have agreed to share best practices and experience with the program with FDA and amongst each other to support the pilot program initiatives and gain a better understanding of QMM.

The information gathered as part of these pilot programs will be used to shape the future of the QMM program but will not impact or influence any regulatory decisions, or inspection planning. OPQ will share aggregated learnings from the pilot programs with the public through workshops and conferences.

OPQ will use the information learned from the two pilot programs along with other previous and ongoing research to formalize criteria that can be used in an assessment tool to objectively measure a manufacturing site's QMM. Data from assessments will be curated into FDA data systems to allow for further analysis and use.

Seven manufacturing sites have been selected to participate in the domestic pilot and seven in the foreign pilot. FDA's multi-center working group is currently engaged with the two contractors for the pilot programs in development of the assessment tools. Site assessments are expected to begin in May 2021 with the final close-out of the pilot programs at the end of September 2021. More information can be

found on the FDA webpage, *https://www.fda.gov/drugs/news-events-human-drugs/sbia-webinar-fda-announces-quality-management-maturity-programs-11122020-11122020.*

PREPARED STATEMENT OF MARY DENIGAN-MACAULEY, PH.D., DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE

Drug Safety: COVID–19 Complicates Already Challenged FDA Foreign Inspection Program

WHY GAO DID THIS STUDY

The outbreak of COVID–19 has called greater attention to the United States' reliance on foreign drug manufacturers and further highlighted the importance of ensuring a safe pharmaceutical supply chain. Much of the manufacturing of drugs for treating COVID–19 occurs overseas, which is also true of the majority of other drugs marketed in the United States. While the volume of drugs manufactured overseas for the U.S. market is not fully known, FDA reports that about 70 percent of establishments manufacturing active ingredients and more than 50 percent of establishments manufacturing finished drugs for the U.S. market were located overseas, as of August 2019.

FDA is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are produced, and conducts inspections of both foreign and domestic drug manufacturing establishments.

GAO has had longstanding concerns about FDA's ability to oversee the increasingly global pharmaceutical supply chain, an issue highlighted in GAO's High Risk Series since 2009. In particular:

- GAO recommended in 2008 (GAO–08–970) that FDA increase the number of inspections of foreign drug establishments.
- GAO found in 2010 (GAO–10–961) that FDA continued to conduct relatively few foreign inspections than domestic inspections.
- GAO found in 2016 (GAO–17–143) that FDA was conducting more of these foreign drug inspections, and GAO closed its 2008 recommendation to conduct more foreign inspections. However, GAO also reported that FDA may have never inspected many foreign establishments manufacturing drugs for the U.S. market.

In addition, in the summer of 2018, FDA began announcing recalls of blood pressure medications manufactured overseas that were tainted with a potential carcinogen, raising further questions about FDA's oversight of foreign-manufactured drugs.

This statement is largely based on GAO's December 2019 testimony (GAO–20–262T) and discusses:

1. The number of foreign inspections FDA has conducted;
2. Inspection staffing levels; and
3. Challenges unique to foreign inspections.

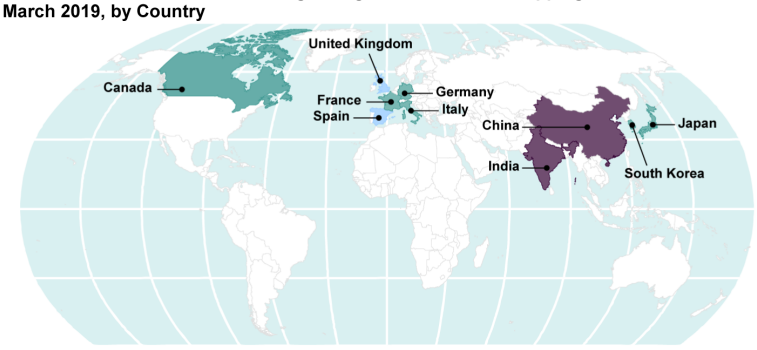
For that testimony, GAO examined FDA data from fiscal years 2012 through 2018 and interviewed investigators from FDA's 2019 cadre of investigators (who are based in the United States but exclusively conduct foreign drug inspections) and from FDA's foreign offices in China and India.

WHAT GAO FOUND

In December 2019, GAO found that a growing number of foreign drug manufacturing inspections conducted by the Food and Drug Administration (FDA) were in China and India (43 percent in 2018), where most establishments that manufacture drugs for the United States were located. In fiscal year 2015, FDA, for the first time, conducted more foreign inspections than domestic inspections. However, from fiscal year 2016 through 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively. FDA officials attributed the decline, in part, to vacancies among investigators available to conduct inspections. In March

2020, FDA announced that, due to Coronavirus Disease 2019 (COVID–19), it was postponing almost all inspections of foreign manufacturing establishments. While FDA has indicated it has other tools to ensure the safety of the U.S. drug supply, the lack of foreign inspections removes a critical source of information about the quality of drugs manufactured for the U.S. market.

The 10 Countries with the Most Foreign Drug Establishments Shipping to the United States as of March 2019, by Country



Number of manufacturing establishments

More than 400 | 100-400 | 70-99

Source: GAO analysis of Food and Drug Administration data (data); National Atlas (base map). | GAO-20-626T

GAO also found that FDA had vacancies among each of the groups of investigators who conduct foreign inspections. FDA had 190 investigators in the United States who conduct the majority of foreign inspections, but an additional 58 positions were vacant. At the time of GAO's December 2019 testimony, FDA was in the process filling 26 of these vacancies, with 32 remaining. However, according to FDA officials, it could be 2 to 3 years before new staff are experienced enough to conduct foreign inspections. FDA also faced persistent vacancies among investigators in its foreign offices.

GAO further found in December 2019 that FDA investigators identified persistent challenges conducting foreign inspections, raising questions about the equivalence of foreign to domestic inspections. Specifically, GAO found:

- While FDA inspections performed in the United States were almost always unannounced, FDA's practice of preannouncing foreign inspections up to 12 weeks in advance may have given manufacturers the opportunity to fix problems ahead of the inspection. Investigators from FDA's China and India offices had conducted some unannounced inspections, but these staff do not perform most of the inspections in these countries (27 percent and 10 percent, respectively).

FDA Estimates of the Amount of Notice Provided to Foreign Drug Establishments Prior to Inspection, Fiscal Year 2018

Type of investigator	Amount of notice provided	Percentage of inspections involving this investigator type
China office investigator	0–5 days	Involved in 27 percent of total number of inspections in China
India office investigator	0–5 days	Involved in 10 percent of total number of inspections in India

FDA Estimates of the Amount of Notice Provided to Foreign Drug Establishments Prior to Inspection, Fiscal Year 2018—Continued

Type of investigator	Amount of notice provided	Percentage of inspections involving this investigator type
U.S.based investigator	Generally 12 weeks	Involved in: • 73 percent of total number of inspections in China • 90 percent of total number of inspections in India • 100 percent of total number of inspections in other foreign countries

Source: Interviews with Food and Drug Administration (FDA) officials and GAO analysis of FDA data. | GAO–20–626T.

- FDA was not generally providing translators on foreign inspections. Rather, FDA continued to rely on translators provided by the foreign establishments being inspected, which investigators said raised questions about the accuracy of information FDA investigators collected. For example, one investigator said there was more risk of conflict of interest if the establishment used its own employees to translate. In addition, the establishment representative providing the translation may be someone who does not have the technical language needed, which can make it harder to communicate with establishment staff and facilitate the inspection.
- The overseas travel schedule can present challenges for FDA's domestically based investigators, who conduct the majority of foreign inspections. Domestically based investigators told us there is little flexibility for them to extend foreign inspections during an overseas trip. The inspections they conduct on an overseas trip are scheduled backto-back in 3-week trips and may involve three different countries. Therefore, extending one inspection would limit the amount of time the investigator has to complete their other scheduled inspections. FDA officials said that inspections conducted by investigators based in China or India (and domestic inspections in the United States) are generally scheduled one at a time and can thus more easily be extended if the investigator needs additional time to pursue potential deficiencies. However, these in-country investigators are not involved in the majority of FDA inspections conducted in China or India.

Chairman Grassley, Ranking Member Wyden, and members of the committee:

I am pleased to be here today to discuss our work on the Food and Drug Administration's (FDA) oversight of drugs manufactured overseas.[1] The outbreak of Coronavirus Disease 2019 (COVID–19) has called greater attention to the United States' reliance on foreign drug manufacturers and further highlighted the importance of ensuring a secure pharmaceutical supply chain. Like the majority of other drugs manufactured for the U.S. market, much of the manufacturing of drugs for treating COVID–19 occurs overseas.

We have had longstanding concerns about FDA's ability to oversee the increasingly global pharmaceutical supply chain, an issue highlighted in our High Risk Series since 2009.[2] A critical element in FDA's oversight of overseas manufacturing is the inspections it conducts of foreign manufacturing establishments. For more than 2 decades, we have raised concerns about FDA's foreign drug inspection program. In 1998, and again in 2008, we found that FDA inspected relatively few foreign drug manufacturing establishments—an estimated 8 percent of those subject

[1] Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and include components of those articles. See 21 U.S.C. § 321(g)(1)(B), (D). An active pharmaceutical ingredient includes, among other things, any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. See 21 CFR § 207.1 (2019). In this testimony, we refer both to drug products—drugs in their finished dosage forms—and to active pharmaceutical ingredients as "drugs." Our work focuses on human drugs and not on most biologics, veterinary medicines, or other items or products for which FDA conducts inspections. (Biologics are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines or analogous products, to prevent, treat, or cure human diseases or injuries and are derived from natural sources, such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i); 21 CFR § 600.3(h) (2019).)

[2] See GAO, *High-Risk Series: Substantial Efforts Needed to Achieve Greater Progress on High-Risk Areas,* GAO–19–157SP (Washington, DC: Mar. 6, 2019).

to inspection for our 2008 report—and that challenges unique to foreign inspections influenced the manner in which FDA conducted such inspections.[3] In our 2008 report we recommended that FDA increase the number of foreign inspections it conducts.[4] In 2010, and again in 2016, we found that FDA was conducting more inspections of foreign establishments (inspecting about 11 percent and 21 percent of those subject to inspection for our 2010 and 2016 reports, respectively). However, in 2010 we reported that FDA continued to conduct relatively fewer foreign drug inspections than domestic inspections, and in 2016 we also reported that many foreign establishments manufacturing drugs for the U.S. market may never have been inspected by FDA.[5] In addition, in the summer of 2018, FDA began announcing recalls of blood pressure medications manufactured overseas that were tainted with a potential carcinogen, raising further questions about FDA's oversight of foreign-manufactured drugs.[6]

My remarks today primarily discuss the findings from our December 2019 testimony on FDA's foreign drug inspection program.[7] Accordingly, this statement provides observations on:

1. The number of FDA's foreign inspections;
2. Inspection staffing levels; and
3. Challenges unique to foreign inspections.

For our December 2019 testimony, we analyzed FDA data from fiscal year 2012 through fiscal year 2018 on inspections of foreign drug manufacturing establishments. We also interviewed FDA drug investigators from FDA's 2019 cadre of investigators, who are based in the United States but exclusively conduct foreign drug inspections, and investigators based in FDA's foreign offices in China and in India. More detailed information on our objectives, scope, and methodology for that work can be found in the December 2019 testimony. The work on which this statement is based was conducted in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

BACKGROUND

Globalization of Drug Manufacturing

Drugs sold in the United States—including active pharmaceutical ingredients (APIs) and finished dosage forms—are manufactured throughout the world. According to FDA, as of August 2019 about 70 percent of establishments manufacturing APIs and more than 50 percent of establishments manufacturing finished drugs for the U.S. market were located overseas.[8] As of March 2019, FDA data showed that India and China had the most manufacturing establishments shipping drugs to the

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[3] See GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program,* GAO/HEHS–98–21 (Washington, DC: Mar. 17, 1998) and *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program,* GAO–08–970 (Washington, DC: Sept. 22, 2008).

[4] See GAO–08–970, 43. FDA agreed with our recommendation and then started conducting more foreign inspections and changed how it selects establishments for inspection to ensure that foreign establishments be inspected at a frequency comparable to domestic establishments with similar characteristics. As a result, we closed this recommendation.

[5] See GAO, *Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress is Needed,* GAO–10–961 (Washington, DC: Sept. 30, 2010) and GAO, *Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices,* GAO–17–143 (Washington, DC: Dec. 16, 2016).

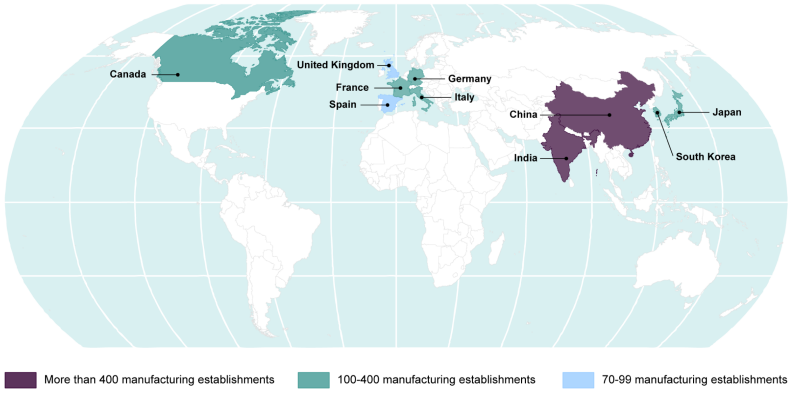
[6] Food and Drug Administration, *FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan),* accessed December 1, 2019, *https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.*

[7] See GAO, *Drug Safety: Preliminary Findings Indicate Persistent Challenges With FDA Foreign Inspections,* GAO–20–262T (Washington, DC: Dec. 10, 2019).

[8] Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration, *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program,* testimony before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, 116th Congress, December 10, 2019. According to FDA, although the agency has information on the location of drug manufacturing establishments, it does not have information on the volume of drug ingredients these establishments manufacture for the U.S. market.

United States, with about 40 percent of all foreign establishments in these two countries. (See fig. 1.)

Figure 1: The 10 Countries with the Most Foreign Drug Establishments Shipping to the United States as of March 2019, by Country



Source: GAO analysis of Food and Drug Administration data (data); National Atlas (base map). | GAO-20-626T

Note: This figure includes the 10 countries with the most foreign drug establishments shipping to the United States and does not include those countries with fewer than 70 establishments. The count of foreign establishments represents the number of establishments that were known to ship or likely would ship a drug to the United States as of March 2019. This count excludes about 380 establishments that participate in some aspect of the manufacturing process, such as sterilizers and analytical labs, but would not ship products to the United States directly. Such establishments are also subject to inspection.

Types of Inspections

FDA is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are manufactured. Drugs manufactured overseas must meet the same statutory and regulatory requirements as those manufactured in the United States. FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, quality, and effectiveness of, and manufacturing processes for, over-the-counter and prescription drugs. CDER requests that FDA's Office of Regulatory Affairs (ORA) inspect both domestic and foreign establishments to ensure that drugs are produced in conformance with applicable laws of the United States, including current good manufacturing practice (CGMP) regulations.[9]

FDA investigators generally conduct three main types of drug manufacturing establishment inspections: preapproval inspections, surveillance inspections, and for-cause inspections, as described in table 1. At times, FDA may conduct an inspection that combines both preapproval and surveillance inspection components in a single visit to an establishment.[10]

[9] CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. See 21 CFR pts. 210, 211, 212 (2019). FDA considers nearly all drug establishment inspections to include an assessment of CGMPs.

[10] Most combined inspections occur when FDA conducts a surveillance inspection at an establishment where a preapproval inspection was also being conducted.

Table 1: Types of Drug Manufacturing Establishment Inspections Conducted by the Food and Drug Administration (FDA)

Type of inspection	Purpose of inspection
Preapproval inspections	FDA conducts preapproval inspections before approving a new brand name or generic drug to be marketed in the United States. These inspections are designed to verify the accuracy and authenticity of drug application data (such as manufacturing records) and assess whether the establishment can manufacture the product in the application in conformance with applicable regulations to assure a drug's identity, strength, quality, and purity.[a]
Surveillance inspections	Surveillance inspections are conducted at establishments when drugs are already marketed in the United States—either after FDA approval or after marketing for drugs that do not require FDA preapproval—and focus on compliance with system-wide controls for ensuring that the manufacturing processes produce high-quality drugs.[b] Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drugs.
For-cause inspections	For-cause inspections are conducted to investigate specific issues, such as those raised in consumer complaints, indications of potential manufacturing problems submitted by the manufacturers themselves, or to follow up on previous FDA regulatory action, among other reasons.

Source: GAO analysis of FDA information. | GAO–20–626T.

[a] When FDA receives an application for drug approval (or a supplement to that application related to a manufacturing change), officials review the inspection history of each establishment listed on the application, among other things. According to FDA officials, if an establishment listed on the application has received a satisfactory good manufacturing practices inspection in the previous 2 years for a similar or more complex product, and the agency has no new concerns, FDA may consider this inspection sufficient and not perform a preapproval inspection of this establishment.

[b] Certain drugs, such as some over-the-counter drugs, may not require FDA approval before marketing in the United States.

FDA uses multiple databases to select foreign and domestic establishments for surveillance inspections, including its registration database and inspection database. Because the establishments are continuously changing as they begin, stop, or resume marketing products in the United States, CDER creates a monthly catalog of establishments. The establishments in the catalog are prioritized for inspection twice each year.

In our 2008 report we found that, because of inaccurate information in FDA's databases, the agency did not know how many foreign drug establishments were subject to inspection.[11] For example, some establishments included in FDA's registration database may have gone out of business and did not inform FDA that they had done so, or they did not actually manufacture drugs for the U.S. market. In our report, we noted that some foreign establishments may register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA, when in fact the establishment may never have been inspected by FDA.[12] We recommended that FDA take steps to improve the accuracy of this registration information. In our 2010 and 2016 reports we found that FDA had taken steps to improve the accuracy and completeness of information in its catalog of drug establishments subject to inspection, such as using contractors to conduct site visits to verify the existence of registered foreign establishments and confirm that they manufacture the products that are recorded in U.S. import records.[13]

To prioritize establishments for surveillance inspections, CDER applies a risk-based site selection model to its catalog of establishments to identify those establishments (both domestic and foreign) that, based on the characteristics of the drugs being manufactured, pose the greatest potential public health risk should they expe-

[11] GAO–08–970.

[12] Foreign and domestic establishments that manufacture drugs for the U.S. market are required to register annually with FDA. Establishments provide FDA with, among other things, their names and addresses and a listing of the drugs that they manufacture for the U.S. market. 21 U.S.C. § 360(b), (i), (j).

[13] See GAO–10–961 and GAO–17–143.

rience a manufacturing defect. This model analyzes several factors, including inherent product risk, establishment type, inspection history, and time since last inspection, to develop a list of establishments that FDA considers to be a priority for inspection.[14] Through this process, CDER develops a ranked list of foreign and domestic establishments selected for inspection that is submitted to ORA. To be efficient with its resources, ORA staff may shift the order of establishments to be inspected on CDER's prioritized list based on geographic proximity to other planned inspection trips, according to FDA officials.

FDA Inspection Workforce

Investigators from ORA and, as needed, ORA laboratory analysts with certain expertise are responsible for inspecting drug manufacturing establishments.[15] FDA primarily relies on three groups of investigators to conduct foreign inspections:

- ORA investigators based in the United States, who primarily conduct domestic drug establishment inspections but may sometimes conduct foreign inspections.
- Members of ORA's dedicated foreign drug cadre, a group of domestically based investigators, who exclusively conduct foreign inspections.
- Investigators assigned to and living in the countries where FDA has foreign offices, who include both staff based in the foreign offices full time and those on temporary duty assignment to the foreign offices. FDA began opening offices around the world in 2008 to obtain better information on the increasing number of products coming into the United States from overseas, to build relationships with foreign stakeholders, and to perform inspections.[16] FDA full-time foreign office staff are posted overseas for 2-year assignments. FDA staff can also be assigned to the foreign offices on temporary duty assignments for up to 120 days. In fiscal year 2019, there were full-time and temporary duty drug investigators assigned to FDA foreign offices in China and India.

Post-Inspection Activities

FDA's process for determining whether a foreign establishment complies with CGMPs involves both CDER and ORA. During an inspection, ORA investigators are responsible for identifying any significant objectionable conditions and practices and reporting these to the establishment's management. Investigators suggest that the establishment respond to FDA in writing concerning all actions taken to address the issues identified during the inspection.

Once ORA investigators complete an inspection, they are responsible for preparing an establishment inspection report to document their inspection findings. Inspection reports describe the manufacturing operations observed during the inspection and any conditions that may violate U.S. statutes and regulations. Based on their inspection findings, ORA investigators make an initial recommendation regarding whether regulatory actions are needed to address identified deficiencies using one of three classifications: no action indicated (NAI); voluntary action indicated (VAI); or official action indicated (OAI).[17] Inspection reports and initial classification recommendations for regulatory action are to be reviewed within ORA. For inspections classified as OAI—where ORA identified serious deficiencies—such inspection reports and classification recommendations are to be reviewed within CDER. CDER is to review the ORA recommendations and determine whether regulatory action is necessary. CDER also is to review inspection reports and initial classification recommendations for all for-cause inspections, regardless of whether regulatory action is recommended by ORA.

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[14] Establishments may also be selected for surveillance inspections for other reasons, such as FDA's focus on a particular product.

[15] ORA investigators lead inspections and are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing. In some instances, staff from CDER, such as subject matter experts or drug application reviewers, may participate in inspections.

[16] Currently, FDA has foreign offices in China, Europe, India, and Latin America but does not have drug investigators in the Europe or Latin America offices.

[17] FDA officials told us that investigators are responsible for checking on previously identified deficiencies in any subsequent inspections of the same establishment. Officials told us that repeated identification of the same deficiency could result in regulatory action.

Inspection classifications are publicly available for some inspections on FDA's website: *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-classification-database/*.

According to FDA policy, inspections classified as OAI may result in regulatory action, such as the issuance of a warning letter. FDA issues warning letters to those establishments manufacturing drugs for the U.S. market that are in violation of applicable U.S. laws and regulations and may be subject to enforcement action if the violations are not promptly and adequately corrected. In addition, warning letters may notify foreign establishments that FDA may refuse entry of their drugs at the border or recommend disapproval of any new drug applications listing the establishment until sufficient corrections are made.[18] FDA may take other regulatory actions if it identifies serious deficiencies during the inspection of a foreign establishment. For example, FDA may issue an import alert, which instructs FDA staff that they may detain drugs manufactured by the violative establishment that have been offered for entry into the United States.[19] In addition, FDA may conduct regulatory meetings with the violative establishment. Regulatory meetings may be held in a variety of situations, such as a follow-up to the issuance of a warning letter to emphasize the significance of the deficiencies or to communicate documented deficiencies that do not warrant the issuance of a warning letter.

THE NUMBER OF FOREIGN INSPECTIONS DECLINED IN RECENT YEARS, AND THE MAJORITY OF SUCH INSPECTIONS IDENTIFIED DEFICIENCIES

Total Number of FDA Foreign Drug Inspections Has Decreased Since Fiscal Year 2016 After Several Years of Increases

In December 2019, we found that from fiscal year 2012 through fiscal year 2016, the number of FDA foreign drug manufacturing establishment inspections increased but then began to decline after fiscal year 2016. In fiscal year 2015, the total number of foreign inspections surpassed the number of domestic inspections for the first time. However, from fiscal year 2016 through 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively. FDA officials attributed this decrease to vacancies in the number of investigators available to conduct inspections (which we discuss later in this testimony statement) and to inaccurate data used to select establishments for inspection in fiscal years 2017 and 2018.

Despite steps taken to improve the accuracy and completeness of FDA data on foreign establishments, in December 2019, we found that the data challenges we identified in our 2008 report continue to make it difficult for FDA to accurately identify establishments subject to inspection. Specifically, since 2017, FDA had pursued an initiative to inspect approximately 1,000 foreign establishments that lacked an inspection history. As of November 2019, officials said all of these establishments had either been inspected or were determined not to be subject to inspection because it was determined they did not actually manufacture drugs for the U.S. market, or had not recently shipped drugs to the United States.[20] However, officials told us that this effort contributed to the decline in the number of foreign inspections conducted because of how data inaccuracies affected the process for selecting establishments for inspection. Specifically, after selecting uninspected foreign establishments for inspection, FDA determined that a sizeable percentage of these establishments were not actually subject to inspection (*e.g.,* about 40 percent of those assigned to the China Office in fiscal years 2017 and 2018).[21] These foreign establishments were thus removed from the list for inspection for the given year. FDA officials told us that the next highest priority establishments identified through the risk-based model to replace those establishments were domestic establishments. As a result, the number of foreign establishments actually inspected decreased. As part of our ongoing work, we plan to examine the accuracy and completeness of information

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[18] Warning letters are publicly available on FDA's website: *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters.*

[19] An import alert can apply to specific drugs or all drugs manufactured by an establishment. Import alerts are publicly available on FDA's website: *https://www.fda.gov/industry/actions-enforcement/import-alerts.*

[20] We previously reported that as of 2016, FDA lacked the inspection history of 33 percent of the foreign establishments in its catalog of establishments subject to inspection.

[21] FDA officials said that some of these establishments were registered with FDA but did not actually manufacture drugs for the U.S. market, and others were drug manufacturers but had not shipped drugs to the United States in the previous 3 years. FDA officials told us that, once identified, they removed such establishments from the catalog of establishments subject to surveillance inspection to which the agency applies its risk-based model each year, but they retained information on these establishments in the larger inventory of establishments should these establishments begin shipping drugs to the United States in the future.

FDA maintains about foreign establishments and the application of its risk-based site selection process.

We further found that FDA continued to conduct the largest number of foreign inspections in India and China, with inspections in these two countries representing about 40 percent of all foreign drug inspections from fiscal year 2016 through 2018. (See table 2.) In addition to India and China, the rest of the countries in which FDA most frequently conducted inspections has generally been the same since our 2008 report.

Table 2: Total Number of FDA Foreign Drug Inspections, by Country, Fiscal Years 2012 through 2018

Country	2012	2013	2014	2015	2016	2017	2018
India	140	110	114	204	207	219	252
China	59	74	113	127	173	165	153
Germany	59	60	72	68	72	69	68
Canada	49	51	39	52	56	72	48
Italy	38	45	50	41	69	46	45
Japan	49	28	47	31	65	46	43
South Korea	4	7	8	5	13	56	40
France	25	37	44	45	55	42	36
Switzerland	23	23	37	31	37	25	32
United Kingdom	29	27	33	43	41	40	12
All other countries	150	175	222	193	247	213	206
Total foreign	**625**	**637**	**779**	**840**	**1,035**	**993**	**935**
Total domestic	**1,184**	**1,030**	**897**	**784**	**882**	**772**	**742**

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO–20–626T.
Note: The total number of inspections includes those conducted for preapproval, surveillance, and for-cause purposes.

Since we last reported on this issue, FDA announced in March 2020 that, due to COVID–19, it was postponing most inspections of foreign manufacturing establishments. Only inspections deemed mission-critical would still be considered on a case-by-case basis.[22] According to the announcement, while the pandemic has added new complexities, FDA has other tools to ensure the safety of the U.S. drug supply. For example, FDA announced that it was evaluating additional ways to conduct its inspectional work that would not jeopardize public safety and would protect both the establishments and the FDA staff. Such ways, according to FDA, could include reviewing the compliance histories of establishments, using information shared by foreign regulatory partners, and evaluating establishment records in lieu of an onsite inspection. In addition, the FDA Commissioner's May 11, 2020 press statement stated that while FDA's regulatory oversight is vital to the long-term health of America, product safety and quality are ultimately the establishment's responsibility.[23] Most firms, according to FDA, strive to reliably provide quality products and maintain the integrity of the supply chain. However, the lack of foreign inspections removes a critical source of information about the quality of drugs manufactured for the U.S. market.

[22] According to FDA, the agency's assessment of mission-critical drug inspections includes consideration for whether the products are innovative breakthrough products or are considered medically necessary. FDA indicated that both for-cause and pre-approval inspections can be deemed mission critical.

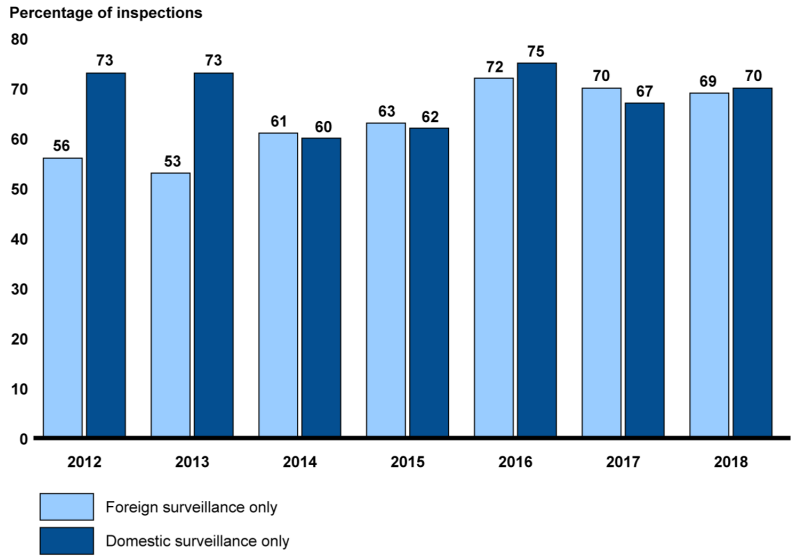
[23] Food and Drug Administration, *Coronavirus (COVID–19) Update: FDA Updates on Surveillance Inspections During COVID–19,* FDA press announcement (May 11, 2020).

It is not clear when FDA will resume regular inspections. The agency originally announced the postponement would last through April 2020. However, on May 11, 2020, it stated that the postponement would continue. According to FDA, the agency continues to closely monitor the global situation. FDA stated that it remains in contact with its foreign regulatory counterparts and would work with the Centers for Disease Control and Prevention to develop a process that would govern how and where to return to on-site facility inspections as conditions improve.

Most Foreign Inspections Were for Surveillance

In December 2019, we found that each year from fiscal year 2012 through 2018 at least 50 percent of FDA's foreign inspections were surveillance inspections. In contrast to preapproval inspections, surveillance inspections are used to ensure drugs already on the market are manufactured in compliance with FDA regulations. In recent years, the proportion of foreign surveillance inspections has increased. As figure 2 shows, in fiscal year 2012, 56 percent of foreign inspections were surveillance-only inspections; in contrast, from fiscal year 2016 through 2018, about 70 percent of foreign inspections were surveillance-only, which was comparable to the percentage for domestic inspections during that period. This is a significant increase from the 13 percent of foreign inspections that were surveillance-only when we made our 2008 recommendation that FDA inspect foreign establishments at a comparable frequency to their domestic counterparts (85 percent of which were surveillance-only at that time).[24]

Figure 2: Percentage of FDA Foreign and Domestic Drug Inspections Conducted for Surveillance Purposes, Fiscal Years 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-626T

Note: FDA conducts surveillance inspections to monitor the ongoing compliance of establishments manufacturing drugs that are already on the market. This figure depicts surveillance-only inspections. FDA conducted additional inspections that had a surveillance component combined with another type of inspection.

In our December 2019 testimony, we also reported that FDA implemented changes to its foreign drug inspection program since our 2008 report that may have contributed to the increase in surveillance inspections. Prior to 2012, FDA was required to inspect domestic establishments that manufacture drugs marketed in the United States every 2 years, but there was no similar requirement for foreign establishments. As a result, and as we reported in 2008, foreign inspections were often

[24] See GAO–08–970, 27.

preapproval inspections driven by pending applications for new drugs. FDA thus conducted relatively few surveillance-only inspections to monitor the ongoing compliance of establishments manufacturing drugs that were already on the market, with just 13 percent of foreign inspections conducted for surveillance purposes at the time of our 2008 report. However, in 2012, the Food and Drug Administration Safety and Innovation Act eliminated the 2-year requirement for domestic inspections, directing FDA to inspect both domestic and foreign establishments on a risk-based schedule determined by an establishment's known safety risks, which was consistent with our 2008 recommendation.[25]

FDA Identified Deficiencies During the Majority of Foreign Inspections

In December 2019, we found that from fiscal year 2012 through 2018, FDA identified deficiencies in approximately 64 percent of foreign drug manufacturing establishment inspections (3,742 of 5,844 inspections). This includes deficiencies necessitating a classification of VAI, or the more serious OAI, as described in the text box.

Inspection Classifications

Based on their inspection findings, FDA investigators make an initial recommendation regarding the classification of each inspection:

- **No action indicated (NAI)** means that insignificant or no deficiencies were identified during the inspection.
- **Voluntary action indicated (VAI)** means that deficiencies were identified during the inspection, but the agency is not prepared to take regulatory action, so any corrective actions are left to the establishment to take voluntarily.
- **Official action indicated (OAI)** means that serious deficiencies were found that warrant regulatory action.

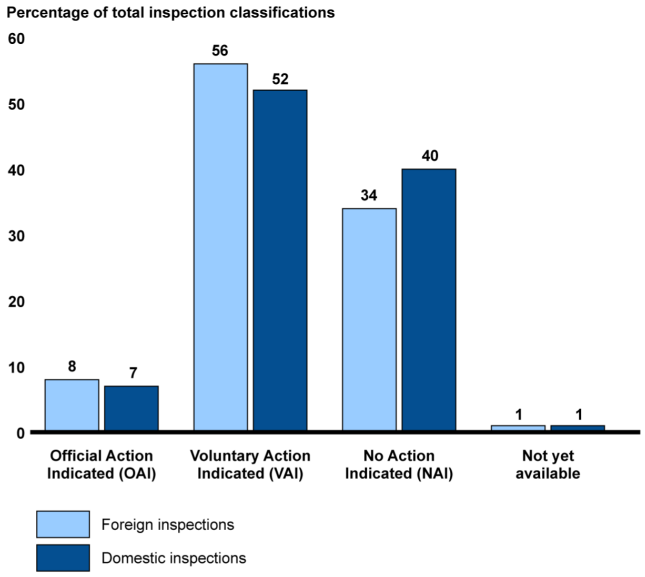
Source: GAO | GAO–20–626T.

About 59 percent of domestic inspections (3,702 out of 6,291) identified deficiencies during this time period. (See fig. 3.) This proportion is similar to what we found when we last looked at this issue in 2008, when FDA identified deficiencies in about 62 percent of foreign inspections and 51 percent of domestic inspections from fiscal years 2002 through 2006.[26]

[25] Pub. L. No. 112–144, § 705, 126 Stat. 993, 1066 (2012) (codified at 21 U.S.C. 360(h)). This established a comparable inspection frequency for foreign and domestic establishments with similar characteristics, consistent with our 2008 recommendation.

[26] In our 2008 report we found that FDA's data did not provide reliable information about the number of foreign inspections with serious deficiencies classified specifically as OAI. Therefore, we reported data on the percentage of inspections classified as either VAI or OAI together. See GAO–08–970, 29. We recommended that FDA correct this issue, and they did so beginning in October 2011, but, for comparison purposes, we continue to report combined VAI and OAI inspection data here.

Figure 3: FDA Inspection Classifications for Foreign and Domestic Drug Establishments by Type of Classification, Fiscal Year 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-626T

Notes: Based on their inspection findings, FDA investigators make an initial recommendation regarding the classification of each inspection: NAI means that insignificant or no deficiencies were identified during the inspection; VAI means that deficiencies were identified during the inspection, but the agency is not prepared to take regulatory action, so any corrective actions are left to the establishment to take voluntarily; and OAI means that serious deficiencies were found that warrant regulatory action, such as issuing a warning letter or import alert.

The analysis presented in this figure is based on 5,844 foreign inspections and 6,291 domestic inspections conducted from fiscal year 2012 through 2018. Totals do not sum to 100 due to rounding. Some classifications were not yet available at the time of our analysis (1 percent of both foreign and domestic inspections). Finally, less than 1 percent of both foreign and domestic inspections received another interim classification, which is not reflected in this figure.

Our December 2019 analysis showed that serious deficiencies identified during foreign drug inspections classified as OAI—which represented 8 percent of inspections from fiscal year 2012 through 2018—include CGMP violations such as those related to production and process controls, equipment, records and reports, and buildings and facilities.[27] For example:

- **Failure to maintain the sanitation of the buildings used in the manufacturing processing, packing, or holding of a drug product (21 CFR § 211.56(a) (2019)).** At an establishment in India producing finished drug products, the investigator reported observing a live moth floating in raw material used in the drug production, and that the facility staff continued to manufacture the drug products using the raw material contaminated by the moth, despite the investigator pointing out its presence.
- **Failure to perform operations relating to the manufacture, processing, and packing of penicillin in facilities separate from those used for other drug products (21 CFR § 211.42 (d) (2019)).** At an establishment in Turkey that manufactured penicillin and other drugs, the investigator reported that the manufacturer had detected penicillin outside the peni-

[27] The identification of serious deficiencies is not unique to foreign inspections. For example, at a domestic establishment producing finished drug products, the investigator observed brown stains, white residues, and brown stagnant water in manufacturing equipment.

cillin manufacturing area of the establishment multiple times. According to FDA, penicillin contamination of other drugs presents great risk to patient safety, including potential anaphylaxis (even at extremely low levels of exposure) and death.

Some investigators who conduct foreign inspections expressed concern with instances in which ORA or CDER reviewers reclassified the investigator's initial inspection classification recommendations of OAI to the less serious classification of VAI.

FDA CONTINUED TO FACE CHALLENGES FILLING VACANCIES AMONG STAFF CONDUCTING FOREIGN INSPECTIONS

In December 2019, we found that FDA's foreign inspection workforce had staff vacancies, which FDA officials said contributed to the recent decline in inspections. As previously mentioned, FDA used multiple types of staff resources to conduct foreign drug inspections—including ORA investigators based in the United States, members of ORA's dedicated foreign drug cadre based in the United States, and investigators assigned to FDA's foreign offices.[28] However, we found that each of these groups had current vacancies. At the time of our December testimony, FDA officials told us that the agency was trying to fill vacancies in each of these groups, but the lower staff numbers may limit FDA's ability to conduct more foreign inspections.

ORA investigators based in the United States. This group of investigators conducted the majority of foreign inspections; about 76 percent of foreign inspections in fiscal year 2018 involved an ORA investigator based in the United States who conducts both foreign and domestic inspections.[29] FDA officials said that the more experienced investigators from this group are expected to conduct three to six foreign inspections per year, and investigators hired using generic drug user fees are expected to inspect nine to 12 foreign establishments per year.[30] As of June 2019, there were 190 investigators eligible to conduct foreign drug inspections, but officials said that as of November 2019, the agency had an additional 58 vacancies in this group. At the time of our December 2019 testimony, officials said that the agency was in the process of hiring 26 ORA investigators based in the United States to fill these vacancies, with 32 vacancies remaining.[31]

FDA officials attributed the vacancies to multiple factors: investigator retirements, investigator movement to other parts of FDA, and the need to hire to additional investigator positions using generic drug user fees. Officials also said that a reorganization within ORA led to a reduced number of investigators who conduct drug manufacturing establishment inspections. While FDA had recently filled several of the vacancies, officials told us that new investigators are not typically used for foreign inspections until they have been with the agency for 2 to 3 years.

ORA dedicated foreign drug cadre. About 15 percent of foreign inspections in fiscal year 2018 involved an investigator from ORA's dedicated foreign drug cadre—a group of ORA investigators based in the United States who exclusively conduct foreign inspections. FDA officials said that members of the cadre are expected to conduct 16 to 18 foreign inspections each year. According to FDA, the cadre had 20 investigators in 2012 and 15 investigators in 2016. However, the cadre had only 12 investigators as of November 2019, out of 20 available slots. At the time of our December 2019 testimony, FDA officials told us that the agency was attempting to fill these positions from the current ORA investigator pool, but officials were not confident that all 20 slots would be filled.

Investigators assigned to FDA's foreign offices. Approximately 7 percent of foreign inspections in fiscal year 2018 involved investigators from FDA's foreign offices. The investigators conducting these inspections were those based in the China and India foreign offices—the countries where most drug inspections occur—and

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[28] In addition to these categories, there are a variety of other FDA staff who, on occasion, may participate in an inspection if certain subject matter expertise is needed.

[29] Inspections can be conducted by one investigator or multiple investigators. Therefore, investigators from more than one group could be involved with a single inspection.

[30] Beginning in 2014, FDA began to use the user fees collected from manufacturers of generic drugs to hire additional investigators focused on inspecting generic drug manufacturers. According to FDA officials, these investigators have primarily been assigned to conduct foreign inspections.

[31] FDA officials indicated that filling these vacancies was a priority for the agency and noted that their recent implementation of direct-hire authority has helped them fill these positions.

also included those investigators on temporary duty assignment to these offices.[32] According to FDA officials, these investigators are expected to conduct 15 foreign inspections each year. We have noted high vacancy rates for these foreign offices in past reports.[33] While these vacancy rates have decreased over time, vacancies persist. As of November 2019, FDA's China office had three of 10 drug investigator positions vacant (a 30-percent vacancy rate), while FDA's India office had two of six drug investigator positions vacant (a 33-percent vacancy rate).

In our December 2019 testimony, we reported that FDA had taken steps to address vacancies in the foreign offices but continued to face challenges. In our 2010 report, we recommended that FDA develop a strategic workforce plan to help recruit and retain foreign office staff.[34] FDA agreed with our recommendation and released such a plan in March 2016, but the long-standing vacancies in the foreign offices raise questions about its implementation. FDA officials told us that one challenge in recruiting investigators for the foreign offices is that well-qualified investigators for those positions need foreign inspection experience. For example, an official in FDA's India office told us that foreign inspections can be challenging, and the India office does not have the resources to develop or train new investigators. Therefore, it is important to recruit investigators who have experience conducting foreign inspections, and such investigators are recruited from ORA. Thus, vacancies in the other two groups of investigators can influence the number of staff available to apply for positions in the foreign offices.

Further, according to FDA officials, after employees have accepted an in-country position, the agency can experience significant delays before they are staffed in the office due to delays in processing assignments. For example, an official in FDA's India office said that investigators need to complete a week-long security training program and must obtain the security clearance needed to work at the U.S. Embassy, which is where FDA's foreign office is located. However, the official told us that there are limited availabilities for that training, and background checks for security clearances can take time.[35] According to this official, FDA investigators did not usually receive first priority for the training. FDA estimated that it can take as little as 1 month to over 2 years for an investigator to clear background and medical checks and arrive at a foreign office. For example, an investigator in FDA's China office told us that as a result of these requirements and other issues, it took nearly 2 years for the investigator to arrive at the office after FDA had accepted the investigator's application. According to FDA's own strategic workforce plan for the foreign offices, these types of delays have resulted in staff changing their decision after accepting a position in the foreign offices.

PERSISTENT CHALLENGES UNIQUE TO FOREIGN INSPECTIONS RAISED QUESTIONS ABOUT THEIR EQUIVALENCE TO DOMESTIC INSPECTIONS

In December 2019, we found that FDA continues to face unique challenges when inspecting foreign drug establishments that raise questions about whether these inspections are equivalent to domestic inspections. Specifically, based on our interviews with drug investigators in the dedicated foreign drug cadre and in FDA's foreign offices in China and India, we identified four challenge areas related to conducting foreign inspections, which are described below. Of the four challenge areas identified, three areas—preannouncing inspections, language barriers, and lack of flexibility—were also raised in our 2008 report.[36]

Preannouncing Inspections. As we reported in 2008, the amount of notice FDA generally gives to foreign drug establishments in advance of an inspection is different than for domestic establishments.[37] Drug establishment inspections performed in the United States are almost always unannounced, whereas foreign establishments generally receive advance notice of an FDA inspection. According to FDA officials, FDA is not required to preannounce foreign inspections. However, they said the agency generally does so to avoid wasting agency resources, obtain the establish-

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[32] The percentage of inspections involving these groups of investigators do not equal 100 percent because some inspections may involve only non-investigator staff, such as CDER drug application reviewers.

[33] See GAO, *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed,* GAO–10–960 (Washington, DC: Sep. 30, 2010), and GAO–17–143.

[34] GAO–10–960.

[35] We have highlighted timeliness concerns with the government-wide personnel security clearance process in our High Risk series. See GAO–19–157SP.

[36] GAO–08–970.

[37] GAO–08–970.

ment's assistance to make travel arrangements, and ensure the safety of investigators when traveling in country.

In our December 2019 testimony, we found that FDA does conduct some unannounced foreign inspections, particularly if the investigators conducting the inspection are based in FDA's foreign offices. However, FDA officials told us that FDA does not have data on the frequency with which foreign drug inspections are unannounced, nor the extent to which the amount of notice provided to foreign establishments varies. According to FDA officials, this is because FDA does not have a data field in its database to systematically track this information.[38] However, the officials estimated that the agency generally gives 12 weeks of notice to establishments that investigators are coming when investigators are traveling from the United States. While investigators in FDA's China and India offices do conduct unannounced or short-notice inspections, these staff do not perform most of the inspections in these countries. (See table 3.)

Table 3: FDA Estimates of the Amount of Notice It Provides to Foreign Drug Establishments Prior to Inspection, by Investigator Type, and the Percentage of Inspections in Which These Investigator Types Are Involved, Fiscal Year 2018

Type of investigator	Amount of notice provided	Percentage of inspections involving this investigator type in fiscal year 2018[a]
China office investigator	Announcement: 0–5 days FDA officials stated that investigators based in FDA's China office will announce surveillance inspections (those related to drugs already on the U.S. market) to drug establishments 5 business days in advance of an inspection. According to FDA officials, for-cause inspections (those conducted in response to specific issues or concerns) conducted by investigators based in the China office are unannounced, meaning that they are not preannounced to the drug establishments in advance.	Involved in 27 percent of total number of inspections in China
India office investigator	Announcement: 0–5 days FDA officials stated that investigators based in FDA's India office will announce inspections to drug establishments 3 to 5 days in advance of an inspection and can conduct short-notice inspections that are announced 30 minutes before the inspection.	Involved in 10 percent of total number of inspections in India
U.S.-based investigator (including dedicated foreign drug cadre)	Announcement: generally 12 weeks FDA officials said that the agency generally announces foreign inspections conducted by domestically based investigators about 12 weeks in advance.	Involved in: • 73 percent of total number of inspections in China • 90 percent of total number of inspections in India • 100 percent of total number of inspections in other foreign countries

Source: Interviews with Food and Drug Administration (FDA) officials and GAO analysis of FDA data. | GAO–20–626T.

[a] These percentages add up to over 100 percent as some inspections may involve more than one type of investigator.

Our work indicated that preannouncing foreign inspections can create challenges and raises questions about the equivalence to domestic inspections. Of the 18 investigators we interviewed, 14 said that there are downsides to preannouncing foreign inspections, particularly that providing advance notice gives foreign establishments

[38] According to FDA officials, FDA planned to add a new variable to its data to identify preannounced and unannounced inspections.

the opportunity to fix problems before the investigator arrives. For example, when an inspection is preannounced, it gives establishments time to clean up their facility and update or generate new operating procedures ahead of the inspection. However, establishments are expected to be in a constant state of compliance and always ready for an FDA inspection, and several investigators told us seeing the true day-to-day operating environment for an establishment is more likely during an unannounced inspection.

Of the 18 investigators we interviewed for our December 2019 testimony, 12 said that unannounced inspections are generally preferable to preannounced inspections. One investigator told us that, although they believed the best way to ensure industry compliance to CGMPs was for establishments to not know when FDA is coming for an inspection, there was no data that would allow the agency to evaluate whether unannounced inspections were better than preannounced inspections. In addition, some investigators told us that it was still possible to identify serious deficiencies during preannounced inspections. For example, investigators could still identify issues by looking at the firm's electronic records, including time-stamped data relating to the creation, modification, or deletion of a record. Three investigators also told us that in some cases there could be benefits to announcing inspections in advance. For example, for preapproval inspections, announcing the inspection in advance gives the establishment time to organize the documentation and staff needed to conduct the inspection.

Language Barriers. Work for our December 2019 testimony indicated that language barriers—which we first reported as a challenge to conducting foreign inspections in our 2008 report—can add time to inspections and raise questions about the accuracy of information FDA investigators collect and thus about the equivalence to domestic inspections.[39] FDA generally does not send translators on inspections in foreign countries. Rather, investigators rely on the drug establishment to provide translation services, which can be an English-speaking employee of the establishment being inspected, an external translator hired by the establishment, or an English-speaking consultant hired by the establishment.

Of the 18 investigators that we interviewed, 14 said that language barriers can be a challenge to conducting foreign inspections and were especially challenging in parts of Asia, including China and Japan. Seven investigators told us this issue was less of a challenge for inspections conducted in other foreign countries, including India and countries in Europe, because workers at establishments in these countries were more likely to speak English, and documentation was also more likely to be in English. Investigators told us that compared to domestic inspections, it can be more challenging and take longer to complete typical inspection-related activities, such as reviewing documentation or interviewing employees, if the investigator needed to rely on translation.

Fourteen of the 18 investigators we interviewed said that there can be concerns related to relying on establishment staff and independent translators. Specifically, 11 investigators told us there can be uncertainties regarding the accuracy of the information being translated, particularly when investigators rely on the translation provided by an employee of the establishment being inspected. For instance, one investigator said that there was more risk of conflict of interest if the establishment used its own employees to translate. Another investigator said that they went to a drug establishment in China that told FDA it had English-speaking employees to translate the inspection, but that was not the case, and the investigator had to use an application on their phone to translate the interviews. In addition, the firm representative providing the translation may be someone who does not have the technical language needed, which can make it harder to communicate with firm staff and facilitate the inspection. One investigator told us that the independent translators hired by firms were sometimes consultants and, in those instances, it can seem like the consultants are coaching the firm during the inspection.

FDA officials told us that when they conduct unannounced for-cause inspections in China, investigators bring locally employed staff who work in FDA's China office to act as translators. The investigators we interviewed said that in such instances, they valued knowing that the translation they were getting was accurate. However, FDA does not have the resources to provide locally employed staff on every inspection, according to an FDA official.

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[39] GAO–08–970.

Lack of Flexibility. Work for our December 2019 testimony indicated that, as we first reported in 2008, the overseas travel schedule can present unique challenges for FDA's domestically based investigators—including both ORA investigators and members of the dedicated foreign dug cadre—who conduct the majority of foreign inspections.[40] Eight of the 12 dedicated foreign drug cadre investigators that we interviewed for our December 2019 testimony told us that there is little flexibility to extend foreign inspections conducted by domestically based investigators, because the inspections they conduct on an overseas trip are scheduled back-to-back in 3-week trips that may involve three different countries.[41] This raises questions about their equivalence to domestic inspections. For instance, extending one inspection would limit the amount of time the investigator has to complete their other scheduled inspections, some investigators told us.

In addition, eight investigators told us that domestically based staff are generally unable to extend the total amount of time spent on an overseas trip—one investigator told us that an investigator would have to find something really bad to justify an extension. In contrast, FDA officials told us that inspections conducted by in-country investigators in China or India, and domestic inspections in the United States, are generally scheduled one at a time and can thus more easily be extended if the investigator needs additional time to pursue potential deficiencies. However, in-country investigators are not involved in the majority of inspections conducted in China or India.

Three investigators from the dedicated foreign drug cadre told us that when they travel overseas, they adjust their inspection approach to help ensure they finish foreign inspections on time. For example, one investigator told us that an investigator may start the inspection in an area of the establishment that was noted as having issues during the last inspection. However, one investigator said that sometimes it is not possible to cover everything in depth during a foreign inspection. Another investigator told us that they focus on identifying the most serious issues during a foreign inspection, and that less serious issues can be identified in the establishment inspection report for reference in the next inspection. Five investigators also noted that they work long hours during their inspection to ensure they can complete the needed work.[42] While FDA may assign more than one investigator to an inspection to complete needed work, one investigator said that FDA does not usually assign more than one person to an inspection because investigators are expected to have the experience to conduct inspections by themselves.

FDA data show that from fiscal years 2012 through 2018, the majority of both foreign and domestic inspections were conducted by one person—77 percent and 66 percent, respectively.[43]

Post-Inspection Classification Process. According to FDA officials, starting in fiscal year 2018, FDA implemented a new post-inspection classification process: when an ORA investigator recommends an OAI classification following an inspection, ORA compliance is required to send that inspection report to CDER for review within 45 calendar days from the inspection closeout. Among other things, the process was intended to help ensure FDA can communicate inspection results to domestic and foreign establishments within 90 days of the inspection closeout, as committed to under the Generic Drug User Fee Amendments of 2017 (GDUFA II).[44] FDA officials told us that the changes also required an additional ORA review for foreign inspection reports to align that process with the process for domestic inspec-

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[40] GAO–08–970.

[41] According to FDA officials, investigators in the dedicated foreign drug cadre are expected to conduct 16 to 18 foreign inspections per year. To meet this expectation, cadre members travel overseas six times a year, with each trip lasting 3 weeks, and conduct two or three back-to-back inspections per trip.

[42] According to FDA officials, members of the dedicated foreign drug cadre can receive up to 15 hours of overtime per week during an overseas week to complete inspection-related work. For example, investigators may use overtime hours to extend the amount of time on site or to review relevant data and documentation when they return to their hotel at night.

[43] In addition to the time pressures associated with sending only one investigator on a foreign inspection, two of the investigators we interviewed from the dedicated foreign drug cadre expressed a preference for conducting team inspections as it helps reduce risks to their personal safety.

[44] Pub. L. No. 115–52, § 301(b), 131 Stat. 1005, 1020 (codified in pertinent part at 21 U.S.C. § 379j–41 note). Prior to each user fee program reauthorization, FDA negotiates with representatives of the generic drug industry to identify goals for how FDA should spend those user fees over the next 5-year authorization period.

tion reports.[45] Although the 45-day reporting time frame for potential OAI classifications is a requirement for both domestic and foreign inspections, adding the additional level of review within ORA effectively shortened the amount of time investigators have to document findings for foreign inspections.

Our work indicated that the post-inspection reporting time frames can create challenges for domestic investigators who conduct foreign inspections and raise questions about the equivalence to domestic inspections. Eight of the 18 investigators we interviewed for our December 2019 testimony said shortening the time for completing reports and adding a level of review has made it more challenging to meet reporting requirements, especially if serious deficiencies are identified during the inspection. Investigators told us that for a potential OAI inspection, they now need to send the inspection report to their supervisor for endorsement within 10 days of the closeout of a foreign inspection, regardless of when the investigator's next inspection is scheduled for, or whether the investigator has to travel from overseas back to the United States after the inspection. For example, if a domestic investigator finds serious deficiencies on the first inspection of an overseas trip—thus indicating an initial OAI classification—the investigator needs to write and send the related inspection report to the ORA supervisor for endorsement before returning home from the 3-week overseas trip to meet the required time frame. One investigator told us that, as a result of the time pressures, post-inspection reports may be less thorough, and that some inspection observations could be better supported if investigators had more time to write the reports.

In conclusion, foreign manufacturing establishments continue to be a critical source of drugs for millions of Americans, and FDA inspections are a key tool to ensure the quality of these drugs. Over the years since we first examined this issue, FDA has made significant changes to adapt to the globalization of the pharmaceutical supply chain and has greatly increased the number of inspections it conducts of foreign establishments. However, we found in December 2019 that the agency faced many of the same challenges overseeing foreign establishments that we identified over the last two decades. These included inspector vacancies and unique challenges when inspecting foreign drug establishments that raised questions about the equivalence of those inspections to domestic inspections. Since then, the outbreak of COVID–19 has added a layer of complexity. It also further highlights the global nature of our pharmaceutical supply chain.

Chairman Grassley, Ranking Member Wyden, and members of the committee, this completes my prepared statement. I would be pleased to respond to any questions that you may have at this time.

QUESTIONS SUBMITTED FOR THE RECORD TO MARY DENIGAN-MACAULEY, PH.D.

QUESTIONS SUBMITTED BY HON. CHUCK GRASSLEY

Question. According to October 30, 2019, testimony from Janet Woodcock, former Director of CDER, "although CDER can describe the locations of API manufacturing facilities, we cannot determine with any precision the volume of API that China is actually producing, or the volume of APIs manufactured in China that is entering the U.S. market, either directly or indirectly by incorporation into finished dosages manufactured in China or other parts of the world." What can the FDA do to bring greater transparency to the supply chain'?

Answer. Congress took a step to fill a gap in FDA's knowledge about the U.S. drug supply chain with the Coronavirus Aid, Relief, and Economic Security (CARES) Act, which was enacted in March 2020. The Act requires domestic and foreign manufacturers to annually report on the amount of each drug manufactured for the U.S. market by each establishment. The new requirement goes into effect in September 2020, and some of its utility will depend on how FDA implements this requirement. We plan to examine the information FDA has on the supply chain of drugs marketed in the United States as part of ongoing work stemming from a request from Senators Schumer and Peters.

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[45] Prior to this change, officials told us that all foreign inspection reports, regardless of classification type, were sent to CDER for review after being endorsed by ORA supervisors. Under the new process, all foreign inspections are reviewed by ORA compliance after being endorsed by ORA supervisors. Foreign inspection reports now only go to CDER compliance for review in certain circumstances, such as if there is an OAI recommended, which had been the process for domestic inspections.

Additionally, in its fiscal year 2020 budget request, FDA included a request for legislation to clarify its authority to require manufacturers to submit information that would improve its ability to assess manufacturing quality and capacity. For example, FDA proposed that manufacturers be required to submit detailed listings for finished drugs or drug ingredients regardless of whether the product was directly imported into the United States or was first sent to another country to be made into a finished drug before being imported to the United States. FDA uses this type of information as part of its selection of manufacturing establishments for inspection. We have ongoing work examining FDA's foreign drug inspection program for the House Committee on Energy and Commerce. As part of that work, we are examining: the extent to which FDA has inspected foreign establishments that the agency considers to be the highest priority for inspection, taken steps to address persistent challenges conducting foreign drug inspections and ensure a sufficient inspection workforce, and taken action to ensure serious deficiencies identified during foreign drug inspections are corrected.

Question. GAO has noted that many administrations have had challenges hiring FDA personnel to work overseas. What actions can FDA take to solve that problem?

Answer. FDA has taken some steps to address its workforce challenges. In our 2010 report, we recommended that FDA develop a strategic workforce plan for its foreign offices to help ensure that the agency is able to recruit and retain staff with the experience and skills necessary for the foreign offices and reintegrate returning staff into FDA's domestic operations. FDA finalized its plan in March 2016, which included key activities to be performed, such as establishing a succession plan for anticipated vacancies, among other things.

In addition, in our 2016 report, we recommended that FDA establish goals to achieve the appropriate staffing level for its foreign offices, which would include separating foreign office vacancies from overall vacancy rates for the Office of International Programs (now Office of Global Policy and Strategy) and setting goals by position type. In June 2018, FDA reported it had separated foreign office vacancies from the Office of International Programs-wide vacancy rate and also set staffing goals by position type, as we recommended. FDA also took other actions, including implementing pay incentives to recruit and retain foreign office staff as well as locality pay for those deployed overseas, and it temporarily assigned staff to short-term rotations in the foreign offices.

However, as we stated in our 2019 and 2020 testimonies, while vacancy rates among investigators assigned to FDA's foreign offices have decreased over time, these vacancies persist. We found that, as of November 2019, FDA's China office had a 30-percent vacancy rate among investigators, while FDA's India office had a 33-percent vacancy rate. FDA officials told us that one challenge in recruiting investigators for the foreign offices is that well-qualified investigators for those positions need foreign inspection experience. Therefore, the agency recruits investigators who have experience conducting foreign inspections from the pool of domestic investigators in FDA's Office of Regulatory Affairs (ORA), including those in FDA's foreign drug cadre. However, the vacancies we identified among both the cadre and this larger group of ORA investigators can influence the number of staff available to apply for positions in the foreign offices. Further, while FDA recently filled several of the vacancies for domestic investigators, officials told us that new investigators are not typically assigned to foreign inspections until they have been with the agency for 2 to 3 years. Therefore, it may be many years before a recently hired investigator is eligible to detail to a foreign office. In addition, the effort to fill vacancies is continuous, as FDA full-time foreign office staff are posted overseas for 2-year assignments, and staff can also be assigned to the foreign offices on temporary duty assignments for up to 120 days. We plan to continue to examine FDA's efforts to ensure a sufficient inspection workforce in our ongoing review of FDA's drug inspection program.

Question. Please describe the benefits to performing unannounced inspections. Would you recommend that FDA implement a policy that makes unannounced inspections standard operating procedure for domestic and foreign inspections?

Answer. According to several of the investigators we interviewed for our December 2019 testimony, a benefit to performing unannounced inspections is that an investigator is more likely to see the true day-to-day operating environment of a drug man-

ufacturing establishment. Most investigators we spoke with told us unannounced inspections are preferable to preannounced inspections.[1]

We also reported in our testimony that FDA's policy to generally announce foreign inspections in advance raises questions about the equivalence of foreign and domestic inspections. Both foreign and domestic drug manufacturers must meet the same regulatory requirements in terms of complying with established quality standards (CGMPs).[2] However-unlike the FDA inspections of drug manufacturing establishments based in the United States, which are usually unannounced-FDA generally preannounces inspections to foreign drug establishments. Although some investigators stated that it was still possible to identify serious deficiencies during a preannounced inspection, the majority of investigators we interviewed said preannounced inspections can give foreign establishments the opportunity to fix some problems in advance of an inspection.[3]

As noted in our 2019 and 2020 testimonies, FDA did not provide us with data on the frequency with which foreign inspections are preannounced and unannounced, nor the amount of notice that is provided when inspections are preannounced. According to FDA officials, FDA does not have these data because its database does not include a field to track whether an inspection is announced or unannounced. FDA officials indicated that FDA had plans to add a new data field to enable the agency to begin tracking whether an inspection is preannounced or unannounced. We are continuing our examination of this issue as part of our ongoing work for the House Energy and Commerce Committee.

Question. What do you believe is behind the FDA's reluctance to implement a policy of unannounced inspections overseas?

Answer. In our 2008 report we found that logistical challenges influenced the manner in which FDA conducted foreign inspections, including announcing foreign inspections in advance. We found that, unlike inspections of domestic establishments which are almost always unannounced, FDA routinely preannounced its inspections to foreign drug establishments. At the time of our 2008 report, FDA was still in the process of opening its overseas offices and solely relied on volunteers from its domestic staff based in the United States to conduct foreign inspections.[4] FDA officials told us that the time and expense associated with conducting foreign establishment inspections required the agency to ensure in advance that establishment staff would be available and that the production line being inspected would be operational at the time of inspection.

In our 2019 and 2020 testimonies, we found that FDA continued to preannounce inspections to foreign drug establishments for the same reason. agency officials estimated that FDA generally notified foreign establishments of an inspection 12 weeks in advance when the investigator conducting the inspection was traveling from the United States-which we found was the case for most of the agency's foreign inspections in fiscal year 2018.[5] According to FDA officials, FDA is not required to preannounce its foreign inspections, but the agency does so partly because of the logistics of traveling overseas and partly because of the cost of conducting foreign inspections. Specifically, FDA officials told us reasons to preannounce foreign inspections include to avoid wasting agency resources, to obtain the assistance of for-

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[1] This is based on our interviews with investigators in FDA's 2019 dedicated foreign drug cadre and investigators based in the agency's China and India offices.

[2] According to FDA, CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities, and adherence to CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations; *https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps* (accessed June 22, 2020).

[3] In addition we reported three investigators told us in some cases, such as for preapproval inspections, there can be benefits to preannouncing inspections as the advanced notice gives establishments time to organize needed documentation and staff for the inspection.

[4] FDA opened its first office in China in November 2008, and its first office in India in December 2008. See *GAO, Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning is Needed,* GAO–10–960 (Washington, DC: Sept. 30, 2010).

[5] We reported that in fiscal year 2018 about 76 percent of foreign inspections involved an investigator based in the United States who conducts both foreign and domestic inspections, and about 15 percent of foreign inspections involved an investigator from FDA' s dedicated foreign drug cadre—a group of investigators based in the United States that exclusively conduct foreign inspections.

eign establishments when making travel arrangements, and to ensure the safety of investigators when traveling in country.

We also noted in our 2020 testimony that FDA does conduct some unannounced or short-notice foreign inspections (*i.e.,* inspections announced no more than 5 days in advance). For instance, FDA officials told us that investigators based in FDA's China office do unannounced inspections when the inspection is being conducted in response to specific issues or concerns (*i.e.,* for-cause inspections), and that investigators in its India office can conduct short-notice inspections that are announced 30 minutes before the inspection or 3 to 5 days in advance. However, we found that foreign office investigators were not involved in the majority of its foreign inspections in fiscal year 2018, and that the agency faced persistent vacancies among available investigator positions in its China and India offices—which are the two countries where FDA continues to conduct the largest number of foreign inspections.

QUESTION SUBMITTED BY HON. PATRICK J. TOOMEY

Question. Was the information required of manufacturers in the CARES Act enough (it required manufacturers to report volume of particular medicines by manufacturing site), or is more data needed for FDA to fully and accurately determine which drugs have particularly vulnerable supply chains?

Answer. The new requirement goes into effect in September 2020, and some of its utility will depend on how FDA implements this requirement. We plan to examine the information FDA has on the supply chain of drugs marketed in the United States as part of ongoing work stemming from a request from Senators Schumer and Peters.

In its fiscal year 2020 budget request FDA included a request for legislation to clarify the agency's authority to require manufacturers to submit information that would improve its ability to assess manufacturing quality and capacity. For example, FDA proposed that manufacturers be required to submit detailed listings for finished drugs or drug ingredients regardless of whether the product was directly imported into the United States or was first sent to another country to be made into a finished drug before being imported to the United States. FDA uses this type of information as part of its selection of manufacturing establishments for inspection. We have ongoing work examining FDA's foreign drug inspection program for the House Committee on Energy and Commerce. As part of that work, we are examining: the extent to which FDA has inspected foreign establishments that the agency considers to be the highest priority for inspection, taken steps to address persistent challenges conducting foreign drug inspections and ensure a sufficient inspection workforce, and taken action to ensure serious deficiencies identified during foreign drug inspections are corrected.

QUESTIONS SUBMITTED BY HON. SHERROD BROWN

TRANSPARENCY AND ACCOUNTABILITY

Question. Based on GAO's work, are there any specific recommendations for enhanced transparency across our drug supply chain—particularly as it relates to APIs—that would facilitate better understanding of the safety of U.S. pharmaceuticals, and potential actions policymakers could take to diversify and protect the safety, quality, and quantity of prescription drugs?

Answer. Congress took a step to fill a gap in FDA's knowledge about the U.S. drug supply chain with the Coronavirus Aid, Relief, and Economic Security (CARES) Act, which was enacted in March 2020. The Act requires domestic and foreign manufacturers to annually report on the amount of each drug manufactured for the U.S. market by each establishment. The new requirement goes into effect in September 2020, and some of its utility will depend on how FDA implements this requirement. We plan to examine the information FDA has on the supply chain of drugs marketed in the United States as part of ongoing work stemming from a request from Senators Schumer and Peters. This work will also examine the barriers to domestic manufacturing and Federal efforts to increase it.

Additionally, in its fiscal year 2020 budget request, FDA included a request for legislation to clarify the agency's authority to require manufacturers to submit information that would improve its ability to assess manufacturing quality and capacity.

For example, FDA proposed that manufacturers be required to submit detailed listings for finished drugs or drug ingredients regardless of whether the product was directly imported into the United States or was first sent to another country to be made into a finished drug before being imported to the United States. FDA uses this type of information as part of its selection of manufacturing establishments for inspection. We have ongoing work examining FDA's foreign drug inspection program for the House Committee on Energy and Commerce. As part of that work, we are examining: the extent to which FDA has inspected foreign establishments that the agency considers to be the highest priority for inspection, taken steps to address persistent challenges conducting foreign drug inspections and ensure a sufficient inspection workforce, and taken action to ensure serious deficiencies identified during foreign drug inspections are corrected.

Lastly, both we and FDA previously reported on potential incentives to address the causes of drug shortages, which may also be relevant to the aim of increasing domestic manufacturing. Specifically, our 2014 report identified multiple potential incentives,[6] including:

- Increasing the transparency of domestic and foreign manufacturing establishments' compliance status, thereby giving manufacturers an additional incentive for the highest quality products and making quality-related supply disruptions less likely to occur.
- Guaranteed purchase , in which the Federal Government guarantees the purchase of a given volume of certain drugs thereby allowing manufacturers to ensure capacity for a given market volume regardless of whether there is sufficient market demand.
- Tax incentives or reductions in FDA fees could also be used to incentivize manufacturers to invest in redundant manufacturing capacity.

FDA also reported similar incentives for addressing drug shortages in a 2019 report.[7] Additionally, we plan on further examining FDA's preparedness and response to drug shortages related to the Coronavirus Disease 2019 (COVID–19) in the near future.

RACIAL AND ETHNIC DISPARITIES

Question. Following up on Senator Carper's line of questioning, can you please elaborate on the investigation and report GAO is planning to put out on COVID–19-related racial disparities? What is GAO's timeline for this report?

Answer. We have a body of published work looking at health disparities in various populations, and we continue to look at issues of racial and ethnic disparities in health outcomes in ongoing GAO work, including work on Coronavirus Disease (COVID–19). For example, we are conducting ongoing work on the availability of data on COVID–19 health outcomes by race and ethnicity as part of our work in response to the CARES Act, Public Law 116–136. This work is expected to be released in August 2020 as part of a larger report covering various topics related to monitoring and overseeing the activities of governmental entities, grantees, contractors, and others in connection with the COVID–19 pandemic. In addition, GAO plans to conduct future work related to racial disparities and COVID–19; however the specific objectives and timing of this work have not yet been determined.

We have also previously reported on the topic of health disparities. For example, in a December 2019 report, we outlined steps the Department of Veterans Affairs (VA) had taken to reduce disparities in health outcomes linked to race and ethnicity but found that the agency lacked mechanisms to mea su re progress and ensure accountability for results . We also reported that VA funds research efforts that have identified disparities in health-care outcomes involving minority veterans but relies on data that VA officials and researchers noted have weaknesses in completeness and accuracy. In March 2020, we also reported on trends in maternal mortality and found that the leading causes of pregnancy-related deaths differed by racial and eth-

[6] Our 2014 report included a synopsis of incentives we identified that were proposed by drug manufacturers and manufacturing associations or included in bills introduced in the 112th Congress and the first 6 months of the 113th Congress, as well as comments from manufacturer and association representatives and FDA. See GAO, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability,* GAO–14–194 (Washington, DC, Feb. 10, 2014).

[7] U.S. Food and Drug Administration, *Drug Shortages: Root Causes and Potential Solutions* (2019).

nic groups. For example, from 2007 through 2016, non-Hispanic black women were more than three times as likely to die than non-Hispanic white women, while non-Hispanic American Indian/Alaska Native women were more than two times as likely to die than non-Hispanic white women. We are conducting ongoing work on maternal mortality and severe maternal morbidity in rural and underserved areas, which is expected to be issued in the Spring of 2021.

Question. Knowing that the availability of timely, standardized data is critical to understanding trends and health outcomes, what are GAO's general recommendations to Federal agencies to improve on the quality, timeliness, and standardization of data reporting and collection? In its work, has GAO identified any areas where legislation or congressional action is necessary to bolster data collection practices?

Answer. GAO has previously reported on the importance of high quality and standardized data and expressed concerns about such data related to health outcomes in a variety of contexts. For example, we previously reported on the importance of quality health outcome data in our December 2019 report on steps VA had taken to reduce disparities in health outcomes linked to race and ethnicity and our March 2020 report on trends in maternal mortality. Most recently, in a review of COVID–19 required by the CARES Act, we determined that the testing data that the Centers for Disease Control and Prevention (CDC) had reported through May 31, 2020, had not provided sufficiently reliable information on the amount of COVID–19 viral testing because these data had been incomplete and inconsistent. CDC acknowledged limitations to these data while maintaining that they were the best testing data available and provided critical insights into how much testing had occurred. We also reported that a recent Department of Health and Human Services (HHS) action could improve testing data. On June 4, 2020, HHS issued guidance that requires all laboratories performing viral or other tests to diagnose a possible case of COVID–19 to submit data for all test results using consistent data elements. Required data also include patients' race, ethnicity, and other demographic information. We will continue to conduct work examining HHS and its component agencies' data reporting related to COVID–19 testing and make recommendations as appropriate.

QUESTIONS SUBMITTED BY HON. BENJAMIN L. CARDIN

NATIONAL SECURITY SUPPLY CHAIN LESSONS

Question. Coronavirus is a wake-up call to the United States to begin to reclaim the control of our medical supply chain.

What are the key lessons we have learned from crises affecting our supply chain and how they may impact national security?

How do we protect our supply chain from these issues?

Looking ahead, how do we diversify the American healthcare system's manufacturing supply chain?

How do we incentivize domestic manufacturing?

Answer. The current Coronavirus Disease 2019 (COVID–19) has heightened the Nation's awareness of the United States' reliance on a global drug supply chain; however, supply chain disruptions affecting the U.S. drug supply are not new and occurred long before the COVID–19 outbreak. The reasons for these disruptions are generally economic in nature. In 2014, we reported on the drug shortage causes that manufacturers reported to FDA. Based on January 2011 through June 2013 data, we found that the most common reasons for drug shortages included quality problems (40 percent), manufacturing delays and capacity issues (30 percent), and issues with active pharmaceutical ingredient (API) or other drug components (9 percent). We also identified potential underlying causes specific to the economics of the generic sterile injectable drug market, such as that low profit margins have resulted in limited infrastructure investments by manufacturers or led some manufacturers to exit the market. In 2019, FDA also reported on the reasons for drug shortages from 2013 through 2017 and similarly found that manufacturing or product quality problems were behind 62 percent of shortages.[8] FDA likewise reported that the root

[8] U.S. Food and Drug Administration, *Drug Shortages: Root Causes and Potential Solutions* (2019).

causes of drug shortages are a lack of incentives for manufacturers to produce less profitable drugs, a market that does not recognize and reward manufacturers for mature quality management systems, and logistical and regulatory challenges that make it difficult for the market to recover after a supply disruption.

Both we and FDA previously reported on potential incentives to address the causes of drug shortages, which may also be relevant to the aim of increasing domestic manufacturing. Specifically, our 2014 report identified multiple potential incentives,[9] including:

- Increasing the transparency of domestic and foreign manufacturing establishments' compliance status, thereby giving manufacturers an additional incentive for the highest quality productions and making quality-related supply disruptions less likely to occur.
- Guaranteed purchase, where the Federal Government guarantees the purchase of a given volume of certain drugs, thereby allowing manufacturers to ensure capacity for a given market volume regardless of whether there is sufficient market demand.
- Tax incentives or reductions in FDA fees could also be used to encourage manufacturers to invest in redundant manufacturing capacity.

In its 2019 report, FDA also reports similar incentives for addressing drug shortages.[10] Additionally, we plan on further examining FDA's preparedness and response to drug shortages related to the Coronavirus Disease 2019 (COVID–19) in the near future.

Lastly, we have ongoing work examining the pharmaceutical supply chain in response to a request from Senators Schumer and Peters. As part of this work, we plan on further examining the barriers to domestic manufacturing and Federal efforts to increase it.

PREPARED STATEMENT OF HON. CHUCK GRASSLEY,
A U.S. SENATOR FROM IOWA

This committee has an obligation to ensure drugs paid for by the taxpayer via Medicare and Medicaid satisfy quality standards and are safe and effective for patients. That responsibility, both of Congress and the FDA, is heightened now that we are living through the COVID pandemic. Whether we are in the midst of a pandemic or not, these supply chain issues must be shored up and solved.

Starting June of last year, I began my oversight activities on this issue. I wrote letters to Secretary Azar and then Acting FDA Commissioner Dr. Sharpless. I asked a series of questions relating to manufacturing facilities overseas that manufacture final dosage form drugs and active pharmaceutical ingredients (APIs). I also asked about how the FDA manages its foreign inspections regime.

The Government Accountability Office has said that the FDA does conduct some unannounced inspections overseas but they don't have data on frequency. However, GAO noted in 2019 that the FDA estimated that they generally provide 12 weeks of notice before the inspection. Simply said, you're undermining the ability of field inspectors to do their job. Twelve weeks is plenty of time to doctor up a facility to make sure that it passes.

Yet, incredibly, some facilities still get caught. That's how bad it is. The end result is that the consumer is put at risk.

According to the most recent FDA data, the United States has 46 percent of finished dosage form facilities. That's where APIs are turned into the final form such as a tablet. That means over 50 percent of sites manufacturing finished drugs are located overseas.

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[9] Our 2014 report included a synopsis of incentives we identified that were proposed by drug manufacturers and manufacturing associations or included in bills introduced in the 112th Congress and the first 6 months of the 113th Congress, as well as comments from manufacturer and association representatives and FDA. See GAO, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability,* GAO–14–194 (Washington, DC, Feb. 10, 2014).

[10] U.S. Food and Drug Administration, *Drug Shortages: Root Causes and Potential Solutions* (2019).

But, that's just part of the story. What we really need to know is, where did the API come from?

According to the most recent FDA data, 13 percent comes from China, and 19 percent comes from India. Combined, that's more than any other country. And overall, more than 70 percent of facilities that make APIs are located overseas. These figures, coupled with the COVID pandemic, have garnered a lot of attention, including what might need to be done from a national security perspective. But, the figures do make clear what needs to be done from a drug safety perspective: we need to have a robust and aggressive foreign inspections program.

Now, with respect to China and India, both those countries have had serious quality control problems. We all remember the valsartan recall where that drug was found to contain contaminants used in rocket fuel. Facilities in China and India produced that drug.

Let's not forget about the Heparin scandal either. In that case, patients undergoing dialysis began to have severe and life-threatening side effects because a manufacturing plant in China introduced a toxin into the production chain. Hundreds of people died and hundreds were sickened.

Then we have Ranbaxy, an Indian manufacturer. Ranbaxy's production chain exposed drugs to potential cross-contamination by penicillin and used APIs from facilities that were not approved by the FDA. Ranbaxy also manufactured Lipitor and was shut down because it could not explain why some of those tablets had pieces of glass in them.

I fear these examples are just the tip of the iceberg. They show why the FDA must maintain an aggressive inspections regime to ensure drug quality but also impose a strong enforcement regime on bad actors. In February of this year, FDA Commissioner Hahn told me that in Fiscal Year 2018 the Center for Drug Evaluation and Research issued almost five times as many warning letters to human drug manufacturers as compared to 2015. He said that's a sign that FDA is better able to use its resources to identify problems. Good. Stay aggressive and don't hesitate to be more aggressive.

On the front end, though, that process should include unannounced inspections overseas. After all, why would we give manufacturers time to prepare their facility for inspection? They ought to be looking over their shoulder every day. That keeps them honest.

During the Obama administration, the FDA started what was called the India Pilot Program. It allowed for no-warning inspections or a couple days' worth of warning. Under it, the FDA issued a 60-percent increase in "Official Action Indicated" findings. In 2015, the Obama administration shut the pilot program down without explanation. It sounds like the program was a victim of its own success.

Now, this issue is bipartisan. Republican and Democrat administrations have come up short. The Government Accountability Office has a body of work from multiple administrations that proves it. For example, both the Obama and Trump administrations have struggled to fill vacancies in foreign offices.

Today, we have witnesses from the FDA who can speak to all of these issues and how the pandemic has impacted their work. On the first panel, we have FDA witnesses and a GAO witness. On the second panel, we have private-sector companies.

It's important to note that I plan to follow up with another hearing soon examining another problematic aspect to our medical supply chain, specifically the increase in trade of fake and faulty personal protective equipment. That is separate from what we will discuss today.

In closing, I want to say two things. First, thank you to the FDA officials who work tirelessly to inspect facilities overseas. Second, regardless of party, we must have an honest discussion of the government's shortcomings so that we can better understand what we, as Congress, can do to ensure drug safety for the taxpayer. After all, we work for them and must always answer to them.

United States Senate

COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

June 27, 2019

The Honorable Alex Azar
Secretary
Department of Health and Human Services

Dr. Norman Sharpless
Acting Commissioner
Food and Drug Administration

Dear Secretary Azar and Acting Commissioner Sharpless:

For decades, safe and affordable drugs have been for sale across our border in Canada, as well as in the United States. I've pressed FDA on importation policies and introduced legislation to help American consumers purchase those drugs. With increasing prescription drug costs, it is important that Americans have options for their much-needed medication. However, unbeknownst to many consumers, the majority of the active pharmaceutical ingredients (API) in drugs they take are produced not in Canada or the U.S., but in China and India. According to recent news reports and a GAO report highlighting safety and quality concerns at foreign drug manufacturing facilities, 80 percent of API are produced abroad, the majority in China and India; however, the FDA only inspected one in five registered human drug manufacturing facilities abroad last year.[1]

This committee has an obligation to ensure that the Food and Drug Administration (FDA) upholds its responsibility to protect the public's health by properly overseeing the Nation's drug supply and ensuring that the drugs Americans use are safe and effective. I am concerned that the FDA's foreign drug inspection program in China and India is not sufficient to identify and address key risks to the health and safety of Americans who rely on these drugs.[2]

For example, a recent *New York Times* article published in May of 2019 calls into question the quality, safety and reliability of brand and generic drugs made overseas.[3] The article chronicles a former FDA consumer safety officer's findings while inspecting foreign manufacturing plants in both China and India from 2012–2018.[4] During the course of his 6 years in those countries, he discovered fraud and deception in 67 of the 86 drug manufacturing plants that he inspected.[5] He routinely uncovered hidden laboratories, fake quality-control, defective sterilization machines and toxic impurities.[6] Equally alarming, the article outlines how, from 2013–2018, the FDA downgraded the regulatory sanctions against more than 100 Indian plants, changing the designation from "official action indicated" to "voluntary action indicated."[7]

An additional news article from NBC News, also published in May of 2019, highlights a different former FDA inspector who also spent time in China and India in-

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[1] Katherine Eban, *Americans Need Generic Drugs. But Can They Trust Them?*, THE NEW YORK TIMES (May 11, 2019), *available at https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html. See also,* U.S. Gov't Accountability Off., GAO–17–143, DRUG SAFETY: FDA HAS IMPROVED ITS FOREIGN DRUG INSPECTION PROGRAM, BUT NEEDS TO ASSESS THE EFFECTIVENESS AND STAFFING OF ITS FOREIGN OFFICES 1 (Dec. 2016). Didi Martinez, Brenda Breslauer and Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.*

[2] Didi Martinez, Brenda Breslauer and Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.*

[3] Katherine Eban, *Americans Need Generic Drugs. But Can They Trust Them?*, THE NEW YORK TIMES (May 11, 2019), *available at https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html*.

[4] *Id.*

[5] *Id.*

[6] *Id.*

[7] *Id.*

specting manufacturing facilities.[8] One plant in Linhai, China, had numerous issues, including anomalies in testing and "unknown impurities." The inspector recommended a warning letter to the facility which would bar it from gaining approvals to produce new drugs at the facility. The FDA reportedly overruled his recommendation.[9] After public criticism of how the FDA handled this case, the FDA said it would have been "unlikely" to catch the impurities at the source of the recall during a routine inspection and that, "our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise."[10]

A Government Accountability Office (GAO) report in December of 2016 revealed that the number of foreign drug facilities that have never been inspected by FDA inspectors was "about 1,000 of the approximately 3,000" foreign manufacturing facilities.[11] Moreover, for fiscal year 2017, the report identified 189 of the 572 facilities in India and 243 of the 535 facilities in China that "may never have been inspected."[12] Lastly, the GAO report detailed, "to address this persistent concern, the agency plans to inspect all establishments in its catalog with no prior surveillance inspection history over the next 3 years (approximately one-third each year), beginning in fiscal year 2017."[13]

Despite the serious concerns with manufacturing quality in China and India, the FDA's data suggests that it does not seem to have sufficiently enhanced scrutiny of those countries. The FDA/CDER Office of Pharmaceutical Quality report from May 2019 suggests that the percentage of inspections in those two countries (22 percent) is on par with the number of facilities in those countries (23 percent)—not an outcome that would suggest increased scrutiny given the reported problems.[14]

The news articles and GAO report are troubling. In order to better understand the scope and nature these issues, please provide written responses to the following questions no later than July 17, 2019:

1. How many manufacturing plants in China and India currently manufacture drugs or APIs intended for the U.S. market?
   a. For each facility, if the facility produces final dosage form drugs, please provide a list of drugs and the corresponding NDAs and ANDAs.
   b. For each facility, if the facility produces API, please provide the name of the API as well as the associated NDAs and ANDAs for the finished dosage form using that API.
2. Please provide a list of all registered manufacturing facilities, either for API or final dosage form drugs, located outside of the United States. In addition, for all drug manufacturing facilities currently registered with the FDA in the United States, China, and India, please provide the following information for all inspections from 2010 to the present:
   a. Facility identifier;
   b. Whether the facility is an API or final dosage form facility;
   c. The API or final dosage form that is manufactured;
   d. Country where the facility is located;
   e. The date of each inspection;
   f. Inspection type;
   g. Whether the inspection was unannounced;
   h. Whether the inspection was conducted by an in-country inspector or an inspector who traveled from the United States or another country;
   i. The initial recommendation of the inspector;[15]
   j. The final FDA recommendation;[16] and a
   k. Description of the resolution to FDA's concerns.

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[8] Didi Martinez, Brenda Breslauer and Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India*, NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.*

[9] *Id.*

[10] *Id.*

[11] DRUG SAFETY, *supra* note 1, at 21.

[12] *Id* at 45.

[13] *Id* at 21.

[14] U.S. FOOD AND DRUG ADMIN., REPORT ON THE STATE OF PHARMACEUTICAL QUALITY 4, 6 (2019), *available at https://www.fda.gov/media/125001/download.*

[15] This request would include official action indicated, voluntary action indicated, and no action indicated results.

[16] *Id.*

3. If a foreign pharmaceutical manufacturing plant used subcontractors or imports API or dosage from other plants, does the FDA inspect these subcontractors or other plants before the primary plant is approved to export to the United States? If not, why not?
4. What criteria does the FDA use to determine which facilities to inspect for an initial inspection? In addition, does a change in ownership trigger a subsequent inspection? Do the criteria differ for API and finished dosage form facilities? Please explain.
5. After the FDA identifies problems at a facility, what steps does the FDA take to ensure that problems are corrected? For example, does the FDA conduct follow-up inspections to ensure that corrective action has been taken? If so, how often are follow-up inspections made to ensure compliance with FDA safety standards? Please provide all records relating to follow-up inspections at manufacturing facilities in China and India from 2010 to the present to the extent they are not covered by Question 2.
6. Does the inspection process in China and India differ from U.S.-based inspections? If so, how and why? In addition, does the approach differ for API and finished dosage form facilities?
7. Please explain the FDA's review process and grading criteria in changing a foreign manufacturing plant designation from "official action indicated" to "voluntary action indicated." In addition, since 2010 to the present, please provide all instances of "official action indicated" being downgraded to "voluntary action indicated" and the rationale for those changes.
8. With regards to the 1,000 foreign manufacturing facilities that the GAO found had not been inspected as of December 2016, how many have been inspected since then? Please provide all records relating to the inspection findings for each facility to the extent they are not covered by Question 2. In addition, has the FDA changed any of its policies to increase the inspection rate at foreign facilities to ensure compliance with safety protocols? If so, please explain. If not, why not?
9. How many FDA personnel and investigative personnel have been stationed in China and India from 2010 to the present? How does it compare to FDA's planned staffing levels?
10. What is the average cost for a foreign inspection for fiscal years 2010–2019?

I anticipate that your written reply and most responsive documents will be unclassified. Please send all unclassified material directly to the committee. In keeping with the requirements of Executive Order 13526, if any of the responsive documents do contain classified information, please segregate all unclassified material within the classified documents, provide all unclassified information directly to the committee, and provide a classified addendum to the Office of Senate Security. Although the committee complies with all laws and regulations governing the handling of classified information, it is not bound, absent its prior agreement, by any handling restrictions.

Thank you in advance for your prompt attention to these matters. Should you have any questions, please contact Joshua Flynn-Brown of my committee staff at (202) 224–4515.

Sincerely,

Charles E. Grassley
Chairman
Committee on Finance

DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

September 24, 2019

The Honorable Chuck Grassley
Chairman
Committee on Finance

United States Senate
Washington, DC 20515–6115

Dear Chairman Grassley:

I write in response to your June 27, 2019 letter requesting information related to the Food and Drug Administration's (FDA) and HHS's efforts to protect the safety of the Nation's drug supply through its foreign oversight program. This first production includes 808 pages of documents bearing bates numbers GrasFDI–000001 to GrasFDI–000809.

Your specific requests for which responsive information or documents are being provided in this production are restated below, in bold type, followed by a description of the documents provided. We continue to collect and review documents responsive to your letter.

1. **How many manufacturing plants in China and India currently manufacture drugs or APIs intended for the U.S. market?**

   a. **For each facility, if the facility produces final dosage form drugs, please provide a list of drugs and the corresponding NDAs and ANDAs.**

   b. **For each facility, if the facility produces API, please provide the name of the API as well as the associated NDAs and ANDAs for the finished dosage form using that API.**

   This analysis was completed using information from the Center for Drug Evaluation and Research (CDER) Catalog of Manufacturing Sites and includes only those facilities involved in manufacturing approved abbreviated new drug application (ANDA) and new drug application (N'DA) products as of June 18, 2019. The list excludes: (1) outsourcing facilities (*i.e.,* facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), facilities that manufacture only excipients (inactive ingredients), and facilities that make drugs for clinical trials only (not subject to routine current good manufacturing practice (CGMP) inspection); (2) certain biologicals for human use that are regulated by the Center for Biologics Evaluation and Research (CBER) (*e.g.,* blood, plasma, and cells/tissues); and (3) facilities that participate in some aspect of pharmaceutical manufacturing but do not ship product to the U.S. (*e.g.,* contracted facilities such as micronizers, sterilizers, repackers, and analytical labs).

   For purposes of this analysis, facilities that manufacture the finished dosage form (FDF) only, or both the active pharmaceutical ingredient (API) and the FDF, have been categorized as FDF manufacturing facilities. Facilities that manufacture only the API for a given drug product have been categorized as API manufacturing facilities.

   Counts of FDF and API manufacturing facilities in China and India that are associated with an ANDA or NDA, and counts of all FDF and API facilities including non-application products, are included in the table below.

Table 1. Counts of All FDF and API CDER Catalogued Facilities Manufacturing Human Drug for the United States (as of June 18, 2019)

Country	Application-related Facilities (NDA and ANDA)	All Facilities (Including Non-Application)
China	180	331
India	339	436

The counts in response to questions 1a and 1b are enclosed.

3. **If a foreign pharmaceutical manufacturing plant used subcontractors or imports API or dosage from other plants, does the FDA inspect these subcontractors or other plants before the primary plant is approved to export to the United States? If not, why not?**

   FDA does not have the authority to license manufacturing plants and cannot "approve" a manufacturing plant for domestic commerce or for export to the U.S. For manufacturing plants that are listed in an NDA, ANDA, or a biologics licensing application (BLA) and that are making an API or FDF, FDA

can and does evaluate the manufacturing plants (facilities) and their operations as described in the applications by evaluating the content of the application and in many cases by reviewing information in our files associated with the facility (or facilities) named in the application that are associated with manufacturing. FDA may also inspect a manufacturing plant identified in the pending application as part of the application assessment effort prior to a decision on approvability. For non-application drug products, such as those that may be legally marketed in conformance with the over-the-counter (OTC) monograph process, the FD&C Act requires manufacturers to notify FDA of their manufacturing operation as it commences to manufacture and distribute a drug in the U.S. market.[1] For manufacturers of OTC monograph products, there is no pre-market assessment of the manufacturing facilities. FDA strives to inspect such facilities as soon as possible after the establishment has registered with FDA.

Facilities that are contracted to perform testing and many other types of operations or controls of the API or FDF in fulfillment of the CGMP requirement[2] are also required to register with FDA and are subject to inspection. FDA expects such arrangements to be described in NDAs, ANDAs, and BLAs, and will evaluate the facilities in these arrangements while assessing the application. The evaluation of a facility may include an inspection.

FDA does not generally know or seek to know the names and addresses of all the suppliers of raw materials (*e.g.,* solvents and reagents) used in API manufacturing operations. However, FDA does expect API manufacturers to identify the names and addresses of sources of key materials, like API starting materials and intermediates, because these, by definition, are key structural fragments of the final API.[3] FDA may inspect such facilities and operations as part of the application assessment. Generally, API starting material and intermediate producers are exempt from annual establishment registration and are not routinely inspected.

For FDFs, FDA does require producers of in-process materials (*i.e.,* materials that are precursors to the final FDF, such as granulated powders intended for compression into tablets or for filling into capsules) to be registered and identified in applications for marketing approval. FDA inspects such operations on a risk-based schedule in accordance with section 510(h)(3) of the FD&C Act using the same site selection process as used for APIs and FDFs. FDA requires FDF repackers, relabelers, and contract sterilizers to register their facilities with the agency, and such facilities are subject to inspection on a risk-based schedule like other facilities.

4. What criteria does the FDA use to determine which facilities to inspect for an initial inspection? In addition, does a change in ownership trigger a subsequent inspection? Do the criteria differ for API and finished dosage form facilities? Please explain.

Any facility that registers their establishment in the FDA electronic drug registration and listing system (eDRLS) is subject to an inspection as soon as possible following initial registration. If the establishment is only associated with a pending NDA, ANDA, or BLA, FDA may conduct a pre-approval facility inspection as part of the application assessment process. If the application is approved, all manufacturing facilities identified in the approved application that are required to register annually with FDA will be included in CDER's Catalog of Manufacturing Sites and subject to a surveillance inspection on a risk-based schedule in accordance with section 510 of the FD&C Act. FDA has a publicly available Manual of Policies and Procedures (MAPP) that describes the agency's risk-based approach to selecting manufacturing sites for CGMP inspections.[4] API and FDF facilities are prioritized for inspection in accordance with the same site selection model; however, generally, FDF facilities are a higher priority than API facilities as there are fewer opportunities to identify a quality problem between the FDF facility's operations and the pa-

[1] See Section 510 of the FD&C Act on establishment registration and product listing requirements.

[2] See Section 501(a)(2)(B) of the FD&C Act and 21 CFR part 211 or 212 for FDFs.

[3] See Internationally Harmonized Guidance (ICH) Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients *(https://www.fda.gov/media/71518/download)* and ICH Q11, Development and Manufacture of Drug Substances *(https://www.fda.gov/media/80909/download)*.

[4] *https://www.fda.gov/media/116004/download*.

tient. FDA CGMP regulations for finished pharmaceuticals obligate the FDF facility to evaluate API suppliers and to test each API shipment, and the CGMP regulations require additional testing of the API during processing and of the FDF before it can be released for distribution.

A change in ownership does not itself trigger an inspection, and certain changes in ownership may not always be known to FDA or known to FDA on/about the time the ownership change is in effect. FDA's expectations for the types of changes an application holder should report are captured in 21 CFR §§ 314.70, 601.12 and further explained in guidance documents.

6. Does the inspection process in China and India differ from U.S.-based inspections? If so, how and why? In addition, does the approach differ for API and finished dosage form facilities?

FDA staff performing facility inspections, whether in the U.S. or abroad, are expected to follow the standard procedures governing inspections, which are in the *Investigations Operations Manual*[5] and the relevant inspection program, or Compliance Program, among other procedural and program documents. Compliance Programs for human drug inspections to evaluate CGMP compliance do not recommend different types of coverage based on country or location. What gets evaluated or covered during an inspection is the same for U.S.- and foreign-based inspections, and depends primarily on the inspection assignment (*e.g.,* for surveillance purpose or for pre-approval purpose), the specific operations at the facility (*e.g.,* API vs. FDF manufacturing, processing vs. testing, sterile vs. non-sterile), and the facility's compliance history (*e.g.,* previous violations or no previous inspection). An inspection team will adjust the inspection strategy based on findings made while on-site performing an inspection.

FDA maintains a Compliance Program specific to APIs,[6] and there are a variety of Compliance Programs for FDFs.[7] The Compliance Program describes very similar approaches to conducting the inspections, which is to permit either an abbreviated or full inspection depending on past FDA inspections, if any, and compliance history and changes to the facility or operations. API inspections are generally planned to take less time than an FDF inspection. FDA additionally maintains a Compliance Program that governs the conduct, approach, and objectives for Pre-Approval Inspections.[8] Further information about our Drug Compliance Programs is available on the FDA website.[9]

10. What is the average cost for a foreign inspection for fiscal years 2010–2019?

The information below includes the average cost to FDA's Office of Regulatory Affairs (ORA) per foreign drug inspection, including travel costs. The inspection costs have been determined by the average hours per inspection based on completed inspections from each fiscal year; the average hours per inspection changes from year to year.

Table 2. Average Cost Per Foreign Drug Inspection

Fiscal Year	Average Cost
FY 2010	$50,700
FY 2011	$56,800
FY 2012	$56,600
FY 2013	$57,100
FY 2014	$55,300

[5] *https://www.fda.gov/media/113432/download.*
[6] *https://www.fda.gov/media/75201/download.*
[7] *E.g., https://www.fda.gov/media/75167/download* (general) and *https://www.fda.gov/media/75174/download* (sterile).
[8] *https://www.fda.gov/media/121512/download.*
[9] *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs.*

Table 2. Average Cost Per Foreign Drug Inspection—Continued

Fiscal Year	Average Cost
FY 2015	$57,400
FY 2016	$65,700
FY 2017	$72,300
FY 2018	$73,800
FY 2019 Est.	$75,400

Please note that by releasing the documents with no redactions to the committee, the Department of Health and Human Services (HHS) is making an accommodation unique to the facts and circumstances of this particular matter; it is not a public disclosure, but instead is a good faith effort to assist the committee in its inquiry. We respectfully request that the committee not disseminate or otherwise disclose these documents outside of the committee without prior consultation with HHS. The production of these materials to the committee does not waive any applicable privilege. For questions, please contact Traci Vitek, HHS Senior Counselor, at (202) 620–7194.

Sincerely,

Traci Vitek
Senior Counselor

cc: The Honorable Ron Wyden, Ranking Member

United States Senate

COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

August 6, 2019

The Honorable Alex Azar
Secretary
Department of Health and Human Services

Dr. Norman Sharpless
Acting Commissioner
Food and Drug Administration

Dear Secretary Azar and Acting Commissioner Sharpless:

This committee has an obligation to ensure that the Food and Drug Administration (FDA) upholds its responsibility to protect the public's health by properly overseeing the nation's drug supply and ensuring that the drugs Americans use are safe and effective. I read with interest your "Safe Importation Action Plan" and am pleased that the administration continues to take steps to address high prescription drug prices while protecting innovation. As you are aware, I believe that drug importation will help to reduce drug costs for American consumers and patients. However, I have also noted that my position is predicated on the FDA ensuring the safety and efficacy of those drugs.

Accordingly, I want to raise concerns with you that I originally raised with the FDA in an oversight letter on June 27, 2019, regarding the FDA's foreign drug inspection program.[1] Unbeknownst to many consumers, according to recent news reports and a GAO report highlighting safety and quality concerns at foreign drug manufacturing facilities, 80 percent of Active Pharmaceutical Ingredients (API) are

[1] Didi Martinez, Brenda Breslauer and Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.*

produced abroad, the majority in China and India; however, the FDA only inspected one in five registered human drug manufacturing facilities abroad last year.[2]

Under the administration's Action Plan, it would draft a Notice of Proposed Rulemaking ("NPRM") that would address, in part, the implementation of section 804(b)–(h) in the Federal Food, Drug, and Cosmetic Act (Act). The Act allows for drug importation as long as certain conditions are met including drug quality, record-keeping, testing, and protections against counterfeiting. The Action Plan notes the "NPRM would list those requirements and invite proposals as to how those conditions would be met by a demonstration project." The NPRM would also allow manufacturers of FDA-approved drugs to import versions of those drugs sold in foreign countries into the United States. However, it is not clear how track-and-trace would apply to such products, potentially exacerbating manufacturing quality concerns.

Since my June 2019 letter to the FDA, I have learned that the FDA does not track in its databases whether a foreign inspection was subject to an announced or unannounced visit. Further, I have learned that the FDA generally does not perform unannounced visits of drug manufacturing facilities in foreign countries but does perform unannounced visits at facilities based in the United States. Should the Action Plan be put into effect, the administration must require more foreign inspections generally and unannounced inspections specifically, particularly compared to previous administrations.

For example, in 2013 the FDA created a pilot program in India that eliminated advanced notice and instead used short notice or unannounced visits.[3] The pilot program also arranged for FDA inspectors' travel to be arranged through the U.S. embassies instead of through FDA offices or manufacturer-arranged travel plans to provide more secrecy in the lead-up to inspections. According to reports, the new inspection regime "exposed widespread malfeasance" that had otherwise been hidden because of the advanced warning system.[4] Among the findings, the inspections found bird infestations, missing samples, and fake laboratories, all of which negatively impact drug quality and safety.[5] Under the pilot program, the FDA issued a 60 percent increase in "Official Action Indicated" findings.[6] In 2015, the pilot program was shut down without explanation.

It is unclear why the Obama administration shut the pilot program down in light of its apparent success. However, because of its reported successes, I strongly encourage the administration's demonstration projects to include unannounced inspections in foreign manufacturing facilities to determine whether they meet the required API and drug quality and safety standards to include sufficient record-keeping, testing, and protections against counterfeiting.

Sincerely,

Charles E. Grassley
Chairman
Committee on Finance

U.S. FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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[2] Katherine Eban, *Americans Need Generic Drugs. But Can They Trust Them?*, THE NEW YORK TIMES (May 11, 2019), *available at https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html. See also,* U.S. Gov't Accountability Off., GAO–17–143, DRUG SAFETY: FDA HAS IMPROVED ITS FOREIGN DRUG INSPECTION PROGRAM, BUT NEEDS TO ASSESS THE EFFECTIVENESS AND STAFFING OF ITS FOREIGN OFFICES 1 (Dec. 2016). Didi Martinez, Brenda Breslauer and Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.*

[3] Katherine Eban, *Bottle X: Exposing Impurities in the Generic Drug Business,* NEWSWEEK MAGAZINE (July 2, 2019).

[4] *Id.*

[5] *Id.*

[6] *Id.*

February 12, 2020

The Honorable Charles E. Grassley
Chairman
Committee on Finance
U.S. Senate
Washington, DC 20510

Dear Chairman Grassley:

Thank you for your letter regarding the Safe Importation Action Plan (Action Plan) and your interest in how the U.S. Food and Drug Administration (FDA or the agency) will ensure the safety and efficacy of drugs imported under the Action Plan. We appreciate hearing from you on this important issue.

As you are aware, in July 2019, the Department of Health and Human Services (HHS) and FDA released the Action Plan to describe steps HHS and FDA will take to allow the safe importation of certain drugs originally intended for foreign markets.[1] The Action Plan describes two pathways to provide safe and effective drugs to consumers in the United States at a lower cost. On December 23, 2019, FDA published the Notice of Proposed Rulemaking (NPRM) and the Notice of Availability for the Draft Guidance associated with each respective pathway.

Pathway 1 involves an NPRM that would implement an importation program under section 804 of the Federal Food, Drug, and Cosmetic Act. The rule, if finalized, would allow importation of certain prescription drugs from Canada under programs sponsored by States or certain other non Federal Governmental entities and authorized by FDA. The NPRM includes requirements to ensure that the importation poses no additional risk to the public's health and safety and that the program will achieve significant cost savings to the American consumer.

Pathway 2 involves a guidance which would provide recommendations to manufacturers for importing FDA-approved drug products they manufactured, and originally intended to sell, in foreign countries. To use this pathway, the manufacturer, or person authorized by the manufacturer, would establish with FDA that the foreign version is the FDA-approved product (*e.g.,* it is manufactured in accordance with the specifications in the FDA-approved application). FDA would then allow the drug to be imported and labeled for sale in the United States. Manufacturers could acquire and use a new National Drug Code for those products, potentially permitting them to offer a lower price compared to what their current distribution contracts require.

Toward the goal of lowering prescription drug prices in the United States, we will be working hard to review comments made to the *Federal Register* dockets for the NPRM and draft guidance and to finalize these documents on an expedited basis.

Your letter also encouraged the use of unannounced inspections and stated that it was unclear how track-and-trace would apply to products under the Action Plan. HHS and FDA understand the vital importance of preserving the drug supply chain's security for continued patient access to safe and effective medicines. Under both proposed pathways outlined in the Action Plan, FDA could take action to protect patients when the agency finds violations of applicable requirements, including those that pose a significant risk to public health.

The U.S. drug supply chain is among the safest in the world. FDA prioritizes domestic and foreign inspections based on the facilities and medicines that have the potential to be the most problematic. The agency inspects drug manufacturing facilities around the world, and 80 to 90 percent of them—regardless of location—are substantially compliant with good manufacturing practice requirements. When FDA identifies manufacturing issues, regardless of whether the facility is located in the United States or elsewhere in the world, we quickly take action to address such issues.

Drug manufacturing has become increasingly complex and global, requiring FDA to remodel its oversight of these tasks to improve the agency's efficiency and reach. In June 2017, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) entered into an unprecedented concept of operations (ConOps) agreement to integrate FDA's facility evaluations and inspections for human drugs.[2] The agreement, *Integration of FDA Facility Evaluation and Inspec-*

[1] See: *https://www.fda.gov/about-fda/reports/fda-safe-importation-action-plan.*
[2] For more information on the ConOps agreement, visit *https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations* and *https://www.fda.gov/media/107225/download.*

tion Program for Human Drugs: A Concept of Operations, outlines the responsibilities and the workflow for pre-approval, post-approval, surveillance, and for-cause inspections at domestic and international facilities. ConOps enables CDER and ORA to effectively manage the growing complexity of the pharmaceutical landscape.

Despite FDA's efforts, there may still be "bad actors" that fail to meet the good manufacturing practice obligations. Over the past 4 years, CDER's Office of Compliance has substantially increased the number of warning letters issued to human drug manufacturers regulated by FDA. For example, in fiscal year (FY) 2018, the agency issued nearly five times as many warning letters to human drug manufacturers as in FY 2015. FDA does not believe that the increased number of warning letters reflects a growing problem in drug quality but instead reflects the agency's ability to better utilize resources to target problem areas. The agency uses "risk-based" targeting to prevent, uncover, and combat data and manufacturing problems.[3]

FDA conducts both domestic and foreign inspections with comparable depth and rigor. For both inspections, the agency uses the same highly trained investigators who conduct each inspection in accordance with the same compliance programs. In many cases, FDA must announce its intention to conduct a foreign inspection in advance to be sure the firm is operational and to avoid wasting inspection resources. However, when the agency determines the need to do an unannounced inspection, FDA can and does conduct such operations. For example, over the past several years, FDA investigators have conducted unannounced inspections at foreign manufacturing facilities in India and China when needed. When significant issues are uncovered at a foreign manufacturing facility, regardless of whether the inspection was announced in advance, the agency acts expeditiously to protect patients by placing the facility on an import alert to block its medicines from reaching U.S. patients.

Although it takes only one bad actor to create a health issue for patients, it is important to note that most facilities and companies pass FDA's inspections and are manufacturing safe, effective, and high-quality medicines. FDA' s laboratory testing for drug quality, using testing standards set by the United States Pharmacopeia or submitted in marketing applications, has consistently shown that medicines manufactured in foreign countries meet U.S. market quality standards.

Thank you again for your interest in this important matter. The agency looks forward to working with you as it executes this plan.

Sincerely,

Stephen M. Hahn, M.D.
Commissioner of Food and Drugs

PREPARED STATEMENT OF HARRY M. LEVER, M.D., STAFF CARDIOLOGIST, SYDELL AND ARNOLD MILLER FAMILY HEART, VASCULAR, AND THORACIC INSTITUTE AT CLEVELAND CLINIC

Thank you, Chairman Grassley and Finance Committee members, for the opportunity to comment. My name is Harry Lever, and I am a cardiologist at the Cleveland Clinic. I am one of the country's leading experts in the treatment of hypertrophic cardiomyopathy, an abnormal thickening of the heart muscle which affects one in 500 people. It can cause shortness of breath, chest pain, dizziness, loss of consciousness, and in a small number of people, sudden death. Many are treated with medication while some require surgery. Early in my career my concern for the quality of generic drugs was occasional. With more generics coming to market and some manufacturing being moved to foreign factories that do not always follow good manufacturing practices, I now have concerns.

Many of the patients that I see are quite fragile and dependent on a combination of medication and surgery. I typically prescribe generic drugs for my patients because they are much less expensive than their brand name counterparts. Insurance companies can often rerequire that I prescribe a generic equivalent as they cost less and are often as just as effective as brand name medications. But I have found that not all generic drugs are of the same quality. I have seen inconsistent results with

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[3] The Office of Pharmaceutical Quality's Manual of Policies and Procedures (MAPP) 5014.1, Understanding CDER's Risk-Based Site Selection Model, outlines the policies and procedures for the Site Selection Model used by CDER staff to prioritize manufacturing sites for routine quality-related (current good manufacturing practice) surveillance inspections. This MAPP is available at *https://www.fda.gov/media/116004/download*.

my patients taking generic drugs in terms of their response to the medication, particularly generic medications coming from countries with poor regulation, such as China and India.

1. DIURETICS TO TREAT CONGESTIVE HEART FAILURE

I have found some diuretics for the treatment of heart failure that do not work adequately. Some of my patients who become stabilized in the hospital and then discharged can have a rapid readmission for heart failure. When I investigated these problems, I found that the patients were given an alternative generic manufacturer of the diuretic that doesn't consistently work. I have also had patients stable for a long period of time on a diuretic and then go into heart failure. Despite my role as the responsible physician, I am typically not informed that a generic substitution was made or told the identity of the new generic medication's manufacturer. The FDA rates generics as interchangeable and these can be changed at any time at a pharmacy. This works as long as the medications are of the same quality—but even the FDA acknowledges that manufacturers need to improve quality.

2. BETA BLOCKERS TO TREAT HYPERTROPHIC CARDIOMYOPATHY, CORONARY ARTERY DISEASE, AND HYPERTENSION

Another drug that I have experienced as a problem is the beta blocker, metoprolol succinate, which is a sustained release drug for the treatment of patients with hypertrophic cardiomyopathy as well as those with coronary artery disease or hypertension. I have found for many patients only the authorized generic or the name brand drug works consistently. In the treatment of hypertrophic cardiomyopathy, at times I have had patients symptoms of shortness of breath, chest pain and dizziness no longer be managed. The question then is am I dealing with a poor quality drug or a patient whose disease is severe and simply is no longer responding to medical treatment? Some patients become symptomatic again for no apparent reason. After checking their drug's manufacturer, I frequently have found that the drug has been changed to a poor quality generic without my knowledge.

3. TRANSPLANT REJECTION MEDICATION

Medications that prevent heart transplant rejections can also be a problem. Colleagues have seen patients who suddenly begin rejecting a new heart after their tacrolimus, a drug used to prevent rejection, is changed to a different manufacturer.

SUMMARY

We need solutions to this problem—I suggest quality ratings that are made public noting which generic products are effective and which should be avoided. More control is needed over the finished product to protect patients. To accomplish this, it will require the medical profession, the drug industry, the insurance companies, and the government working together as partners.

Thank you.

PREPARED STATEMENT OF DAVID LIGHT,
FOUNDER AND CEO, VALISURE

Chairman Grassley, Ranking Member Wyden, and distinguished members of the Senate Finance Committee, thank you for holding this important hearing. My name is David Light, and I am the founder and CEO of Valisure.

At Valisure, our mission is to help ensure the safety, quality, and transparency of medications, and we do this with a very simple but novel approach: we check. Valisure is an online pharmacy attached to an analytical laboratory. We are the first and only pharmacy in America that chemically batch-validates every medication we sell, and we do it at no additional cost to consumers. Founded in 2015, Valisure is headquartered at Yale Science Park in New Haven, Connecticut. Valisure is ISO–17025 accredited by the International Organization for Standardization (ISO) and is registered with the Drug Enforcement Administration (Pharmacy: FV7431137, Laboratory: RV0484814) and the Food and Drug Administration (FDA) (FEI #: 3012063246).

In response to rising concerns about medication quality, counterfeit medications, and overseas manufacturing, Valisure developed proprietary analytical technologies that we use in addition to the FDA's standard assays to test every batch of every

medication we dispense. Valisure tests medications for correct dosage, major inactive ingredients, proper dissolution, and the presence of carcinogens such as N-Nitrosodimethylamine (NDMA). Currently, we reject over 10 percent of on-market medication batches based on these testing standards.

With roughly 80 percent of ingredients in U.S. medications manufactured in India and China,[1] medication quality is constantly called into question. There are roughly three drug recalls in the U.S. every day and about 100 of those recalls every year are "Class I," which are considered potentially life-threatening. These recalls can be attributed, at least in part, to the fact that the chemical quality of medications is primarily checked by manufacturers, which self-report the results. Most manufacturers are located overseas, where oversight by the FDA is difficult and fraud is commonplace. These general difficulties are only made worse by the COVID–19 pandemic.

A useful metaphor for understanding the immense complexity of the drug supply chain and the critical need for independent analysis is to think of a bottle of medication like a used car. When you go to pick up a medication from your local pharmacy, it will often be a year or two old, have traveled thousands of miles, and touched dozens of hands all around the world. No one who buys a used car is satisfied to know that the original manufacturer vouched for its quality. Buyers want a Carfax report; a 100-point inspection on that specific car, or more. None of that transparency is available for medications. To ensure quality, we must do more than just review a manufacturer's paperwork and facilities: we need independent chemical analysis of the medication itself.

In a 2015 FDA white paper, the FDA acknowledged that it "has no formal means for quality surveillance, except through inspections" and conceded that "inspection findings have not been a reliable predictor of the state of quality."[2] The paper also noted that "product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production."

Inspections by FDA at overseas plants are often announced months in advance and are typically conducted less frequently than the inspections of U.S. facilities, which are unannounced.[3] Even these infrequent overseas inspections have been halted as a result of the COVID–19 crisis,[4] making the need for greater oversight and quality assurance of the drugs coming into our country more imperative than ever.

Recent drug quality issues have threatened the health and safety of American consumers, including the widespread contamination of critical blood pressure medications,[5] gastroesophageal reflux disease drugs,[6] and diabetes medications[7] tainted with carcinogens.[8] Not only do drug quality issues place patients' lives at risk, they also account for over 60 percent of drug shortages[9] and generate fear and mistrust that is a contributing factor to medication non-adherence.[10]

We believe Valisure's work has only scratched the surface of the troubling drug quality issues in the U.S. supply chain. In less than a year, Valisure has identified a fourth major carcinogen in valsartan, discovered the fundamental instability of Zantac/ranitidine leading it to break down into a carcinogen, detected high levels of NDMA in roughly 40 percent of analyzed batches of the diabetes drug metformin, and uncovered many other serious issues. The immense impact of and critical need for independent chemical testing of medications has become extremely clear.

THE RECALL OF ZANTAC/RANITIDINE: CASE STUDY IN THE NEED FOR INDEPENDENT CHEMICAL TESTING

The idea of independently checking drug products may be new to industry, but in the academic world, it has been done for decades. However, warnings from academics have unfortunately largely been ignored. A grim but perfect example of this relates to the drug Zantac and its generics, ranitidine.

In 1977, Senators sat in Dirksen Senate Office Building and listened to testimony from the prominent scholar Dr. William Lijinsky, Director of the Chemical Carcinogenesis Laboratory at Frederick Cancer Research Center. Dr. Lijinsky presented strong evidence that certain drugs are unstable and prone to forming the extremely potent nitrosamine carcinogen NDMA. In his opening remarks, Dr. Lijinsky testified:

> Methapyrilene, like many similar antihistaminic drugs, is a tertiary amine. Being a tertiary amine, it reads [reacts] with nitrites in mildly acid solution to form a nitrosamine, dimethylnitrosamine [NDMA], which is one of the most potent carcinogens known, inducing liver cancer in rats.[11]

Like methapyrilene, Zantac is an antihistamine, has a tertiary amine, and it reacts with nitrites (commonly found in many foods) in mildly acid solution (like a full stomach) to form NDMA.

A year later, in 1978, the World Health Organization (WHO) and the United Nations held a global summit on nitrosamine carcinogens[12] where leading scientists from around the world expressed concern about NDMA and its formation from some common drugs.

By 1979, methapyrilene, the drug Dr. Lijinsky used as an example in his testimony, was removed from the market after 25 years of use due to concerns that it was carcinogenic[13] and forming NDMA.[14, 15]

Despite these multitudes of warnings, Zantac/ranitidine, which had practically the same, if not worse, chemical instability and NDMA formation issues, was approved in 1981 in the UK and in 1983 in the U.S.[16] The first of many academic studies raising the possibility of Zantac/ranitidine being carcinogenic were published in 1982 and 1983.[17, 18, 19, 20] Dozens of studies in top journals followed, including clinical[21] and epidemiological studies.[22] Another series of studies started in 1982 and investigated the use of "nitrosatable drugs" (Zantac/ranitidine is highly "nitrosatable") being used during pregnancy and found links to childhood tumors,[23, 24] birth defects,[25, 26] and other serious negative effects.[27, 28] However, the multitude of studies had little, if any, practical impact on the pharmaceutical and regulatory world. Despite the loud warnings from academics, Zantac/ranitidine became one of the best-selling drugs in history[29] and among the most commonly prescribed drugs to treat acid reflux in pregnant women[30] and infants.[31]

It was not until 2019, 38 years after Zantac/ranitidine was first approved and 42 years after Dr. Lijinsky delivered his warnings to the U.S. Senate, that Valisure's analytical pharmacy performed the simple act of independently checking a bottle of generic Zantac syrup prescribed to one of our co-founder's infant daughter. The results were so dramatic that we immediately took the drug off our formulary and tasked our full scientific staff to investigate.

After we realized the magnitude of the problem, we were not satisfied by simply publishing our findings in a scientific journal. We petitioned the FDA directly;[32] we spoke to press; and we did not back down from the crystal-clear science that Zantac/ranitidine is fundamentally unstable, forms a potent carcinogen, and should be taken off the market. Two months ago, after dozens of countries had already banned the drug,[33] the FDA finally granted our petition,[34] and this potentially dangerous drug was officially taken off the U.S. market.[35]

Without independent testing and the drive to make it broadly transparent and recognized, Zantac/ranitidine could have remained on the market for many more decades to come.

THE PREVALENCE OF CONTAMINANTS IN MEDICATIONS IN THE U.S. SUPPLY CHAIN

Valisure's investigation into Zantac/ranitidine's link to NDMA was a result of our general interest in analyzing medications for carcinogens, which began as a response to the rampant recalls of the blood pressure medications valsartan, losartan, and irbesartan. These recalls, which began in the summer of 2018, eventually expanded to over 1,000 lots of the sartan class of drugs from numerous manufacturers due to the presence of NDMA and other similar nitrosamines.[36]

While there are an infinite number of possible impurities that a laboratory could test medications for, some, like NDMA, are obvious. NDMA has been studied in medications for decades,[37] and the technology to detect it down to parts per billion and beyond has been widely available since at least 1970.[38, 39]

Other commonplace carcinogens are also logical to investigate, such as N,N-Dimethylformamide (DMF). DMF is an industrial solvent that was reclassified in 2018 by the WHO and International Agency for Research of Cancer (IARC) as a Group 2A "probable human carcinogen," the same category as NDMA. The FDA classifies DMF as a Class 2 solvent, which "should be limited in pharmaceutical products because of their inherent toxicity."[40] However, DMF is nonetheless used in the production of pharmaceutical active ingredients, including valsartan. Residual solvents are known issues in pharmaceutical processing, and, because DMF was

implicated as a source of NDMA formation in valsartan, it was one of the first impurities to be added to Valisure's standard impurities analysis. As soon as we started looking for DMF, we found it.

Valisure tested over 30 batches of valsartan medications and found that approximately two-thirds contained high levels of DMF. We included these findings in a Citizen Petition filed with the FDA on June 13, 2019.[41] Our analysis suggests that although progress has been made to reduce NDMA in -sartan medications, even after 2 years of recalls, the fundamental manufacturing processes have not been significantly improved. In the absence of independent scrutiny and regulatory action, manufacturers continue to be motivated to use cheap solvents like DMF rather than investing in improving drug quality and safety.

Valisure's analysis found DMF not just in medications produced by generic manufacturers but also in Diovan, the branded version of valsartan produced by Novartis. This finding illuminates the immense complexity of the drug supply chain and the difficulty faced even by manufacturers who are proactive about ensuring quality. A spokesperson for Novartis provided the following comment to *Bloomberg News* regarding the DMF finding:

> "Novartis doesn't use DMF in making Diovan and documents provided by suppliers it purchases ingredients from indicate that they don't, either," said spokesman Althoff. "But companies that its suppliers buy from could."[42]

The vast and incredibly complex web of the pharmaceutical manufacturing industry has been recognized as a danger for many years, but it has resisted a slew of new technologies that attempted to "secure it."[43] Therefore, independent, proactive chemical analysis of medications that is made transparent to all in the health-care ecosystem is critical,and not just for generic manufacturers in a handful of overseas countries, but as an overall industry standard.

METFORMIN: A CURRENT CRISIS FOR ROUGHLY 18 MILLION TYPE 2 DIABETICS IN THE U.S.

Metformin is an oral diabetes medication that helps control blood sugar levels in adults and adolescents with type 2 diabetes. Metformin is taken by over 18 million Americans and is prescribed over 90 million times a year, making it the fourth-most prescribed drug in the U.S.[44]

Amid actions by regulators worldwide to step up vigilance on drug quality, the Ministry of Health of Singapore was the first to publicly identify NDMA contamination in metformin and issued recalls in early December 2019.[45] Switzerland announced recalls weeks later[46] and, by February 2020, Canada had followed suit.[47]

The FDA announced it would investigate metformin contamination in December 2019.[48] In February 2020, the FDA released a laboratory method for the analysis of metformin[49] and published lab results.[50] The FDA reported that it had analyzed 16 batches of metformin from seven companies and found no NDMA beyond acceptable levels. However, it is important to note that the FDA may have acquired the medication samples through voluntary submission direct from manufacturers, which can introduce significant sampling bias and would not be an independent measure of quality.

To independently evaluate the state of metformin contamination, Valisure acquired 38 batches of metformin from 22 companies through our pharmacy's distributors. The results from this analysis were included in a FDA Citizen Petition filed on March 2, 2020.[51] In our analysis, Valisure utilized the FDA's published testing protocol but modified it to improve sensitivity and, importantly, to add an internal control.[52] Our results showed that 42 percent of the batches analyzed (16 of 38) contained NDMA exceeding the FDA's daily acceptable intake limit, with the highest detected amount over 16 times the permissible limit. To further validate this data, Valisure sent samples from a contaminated batch of metformin to be independently verified by Emery Pharma, an FDA registered/inspected, cGMP/GLP compliant analytical laboratory.[53] Emery's results showed slightly higher NDMA levels than what Valisure found, confirming the severity of the contamination.

Valisure's analysis of its pharmacy batches significantly widened the number of sampled products and companies beyond the FDA's original report and likely reduced the sampling bias but was still limited by the availability of the drug from Valisure's pharmacy distributors. Therefore, Valisure conducted a direct-to-consumer crowdsourcing study in which we called for individuals to send us samples

of metformin for free analysis. This effort resulted in the evaluation of 128 samples of metformin from individuals located in 30 States. The results of Valisure's analysis of these samples were detailed in a study co-authored with a researcher at The University of Maryland School of Pharmacy and posted on medRxiv.org, a pre-publication server maintained by Yale University.[54] As summarized in the study abstract,

> 42 percent of all medication samples contained detectable levels of NDMA and, when scaled to maximum daily tablet dose, 36 percent of all medication samples contained NDMA levels exceeding the FDA daily acceptable intake limit. The highest NDMA detection from the tested samples was 1565 ng per tablet, which, when commonly taken four times a day, is 65 times the United States Food and Drug Administration (FDA) acceptable daily intake limit. Results underscore the need for immediate product recalls of tainted medications and an overall investigation of metformin manufacturing practices.

These results largely mirror the findings from the analysis of pharmacy samples in Valisure's FDA Citizen Petition, and again illustrate the importance of independent testing derived from independently sourced samples.

The FDA recognized the importance of Valisure's Citizen Petition, and, in response, requested samples from the batches we analyzed. On April 1, 2020, Valisure voluntarily supplied tablets from each of the 38 identified batches. On May 28, 2020, the FDA announced that it was in contact with five metformin manufacturers and was urging them to voluntarily recall their products.[55] It appears that this action was spurred in large part by the agency's analysis of the samples provided by Valisure. Valisure applauds this decision and hopes there will be future opportunities for collaboration between the FDA and independent laboratories like ours. However, a disconnect regarding the severity and breadth of the metformin contamination issue unfortunately persists due to discord over analytical methodologies.

In the case of metformin, the current FDA statements target only the extended release (ER) formulations of metformin, which account for about one quarter of prescriptions,[56] and not the immediate release (IR) formulations, which have also been identified by Valisure to contain unacceptable levels of NDMA. Furthermore, the agency states that their findings of NDMA in metformin "were generally lower than reported by the private laboratory [Valisure]." Both these discrepancies are likely explained by the agency's published method for the analysis of metformin not including an internal control.

Internal controls are considered scientific best practice by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[57] and are industry standard for the analysis of NDMA in complex samples like drinking water,[58] wastewater,[59] soil,[60] food[61] and beverages,[62] biological samples,[63] and pharmaceutical products[64] (including Singapore's published method for NDMA analysis in metformin[65]).

To understand the importance of an internal control more simply, it is useful to employ the metaphor of taking a picture of a fish to show its size. To properly portray the size of the fish, one can place a penny or a dollar bill next to it. The penny is acting as an "internal control" because it is a known size, so now a person can properly appreciate the size of the fish in the picture.

In Valisure's study of metformin, the internal control was highly influential to obtain proper quantification of NDMA and the internal control had the greatest influence on IR tablets.[66] This implies that without the use of an internal control, NDMA levels will incorrectly appear significantly lower overall and, in particular for IR formulations, potentially to the point that unacceptable levels of contamination may not be detected at all in IR tablets if the control is not used.

These details may sound overly technical, but the consequences are profound. While debate ensues over analytical methodologies, roughly 13 million Americans are currently taking IR formulations of metformin and are at risk of continued exposure to unacceptable levels of NDMA. This situation is very similar to what occurred with Zantac/ranitidine nearly a year ago, in which the product remained on the market for months while the FDA contested analytical techniques.

Another critical component of the importance of independent analysis is the flexibility to improve upon regulatory guidance for analytics which may not always follow the latest best practices.

PROPOSED SOLUTIONS: CERTIFIED DRUGS, DRUG QUALITY SCORES, AND REGULATORY INTERVENTIONS

While the problems with the U.S. supply chain are significant, we believe there are several straightforward steps that would either stop these issues before products even leave the manufacturing plant or enable immediate, real-time action by buyers and payers to avoid purchasing low-quality products.

Certified Drugs

As aforementioned, Valisure conducts batch-testing of every product dispensed to our customers before it leaves the pharmacy, and we do so without adding any cost to patients. We believe this could be replicated on a larger scale, creating "certified drugs" that are independently chemically analyzed and certified before being sold to a patient, pharmacy, wholesaler, or health-care system.

Ideally, this independent analysis would be done immediately after the original manufacturer produces the product, when the full size of the batch is in one location and before the product is dispensed to wholesalers and other down-market entities. The results of this analysis—in the form of a simple certificate—could be a desired, value-add mark that follows the product through the supply chain and into the hands of the patient receiving the medication, thus ensuring transparency and recognition of quality.

This independent analysis is already possible at less than a penny per pill at Valisure's pharmacy, and the cost could easily be borne by manufacturers or large entities in the supply chain. Manufacturers could stand to gain market share for these certified products either by standard market drivers or through new requirements or incentives by health systems and large private or government purchasers.

Health systems are constantly plagued by drug quality issues and are impacted both tangibly (*e.g.,* drug recalls) and intangibly (*e.g.,* doctor and pharmacist time dealing with recalls; patient mistrust; readmissions; poor treatment of patients' conditions). Leading health centers like the Cleveland Clinic have identified so many issues that "Cleveland Clinic pharmacists developed a confidential black list of drugs it would no longer buy."[67] Prominent health systems or other major entities in the drug supply chain that are concerned about quality and patient safety could demand certified drugs and either require or incentivize having independent certification in their purchasing processes.

Certified drugs not only have the advantage of removing potentially dangerous products from the market but would inject much-needed transparency into the U.S. drug supply chain. As noted by Professor John Gray of Ohio State University in a statement submitted for the record for this hearing:

> Unlike many consumer products, consumers/patients generally cannot know if there is a problem with their drug by looking at it. Further, even after taking the drug, it is hard to pinpoint that any side effects are the result of drug quality. This lack of quality visibility makes testing more critical in the drug industry than in many other industries. It also increases the risk that manufacturers, facing cost and delivery pressures, allow drugs to be shipped that did not meet all process and/or product specifications.

The opacity of drug quality and the difficulty it can cause providers is exemplified by the many clinical examples observed by distinguished doctors at the Cleveland Clinic.[68] In the book *Bottle of Lies* by Katherine Eban, a whole chapter is dedicated to a term coined by a Cleveland Clinic doctor called "the X factor":

> visualize each patient's case as an algebraic equation. A new symptom put an unknown variable, an "X," into the equation . . . generics seemed to be a new X that threw off the whole equation.

In other words, potential quality problems resulting from drug manufacturing present a further "X factor" that can frustrate proper diagnosis and treatment. As such, the visible mark of quality a certified drug offers would provide immense value to patients, doctors, payers, and the broader health-care system.

Drug Quality Scores

Although we believe that Valisure's independent chemical analysis of pharmaceuticals could be replicated on a larger scale, in the near term, certified drugs are likely only realistic for a handful of high-volume, high-impact drugs. However, data is available today that provides valuable insights on practically all drug products in the U.S.

On February 3, 2020, Valisure had the honor to be a plenary speaker at an event hosted by the Duke Margolis Center for Health Policy in partnership with FDA, *Understanding How the Public Perceives and Values Pharmaceutical Quality.*[69] At this event, a broad group of leaders from health-care systems, the pharmaceutical supply industry, payers, universities, and non-profits strongly agreed there is a troubling lack of transparency into medication quality, and that the development of medication "quality scores" would be a powerful solution.

The FDA's Task Force on Drug Shortages has endorsed the creation of a voluntary "rating system. . . . to inform purchasers, group purchasing organizations (GPOs) for health-care systems, and even consumers, about the quality management maturity of the facilities making the drugs."[70] We believe that this would be an important first step. However, data on quality management maturity—in other words, a manufacturer's paperwork—falls far short of the transparency on drug quality demanded by supply chain stakeholders.

Independent quality rating systems should be developed through a process that includes robust stakeholder feedback, including patients, providers, academic institutions, and health systems. These ratings systems should rely on objective, science-based data that is not solely voluntarily provided by manufacturers but generated by independent third parties. To accomplish this, results from independent chemical analysis of drug products could be combined with publicly available regulatory data and turned into drug quality scores that could be as simple as a "red/yellow/green" rating for each drug made by each manufacturer. Any buyer or payer could simply strive to buy green, occasionally yellow, and just avoid red.

A recent paper, *Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems,*[71] (Attachment B) written by authors from NYU Langone Health, Columbia University, Defense Health Agency, University of Utah Health Care, Cleveland Clinic, Yale School of Public Health, and University of Connecticut School of Pharmacy, illustrates how such an independent system of quality ratings could work. Valisure contributed data and expertise to this paper. As explained in the extract:

> The quality of drug products in the United States, which are largely produced overseas, has been a matter of growing concern. Buyers and payers of pharmaceuticals, whether they are health-systems, insurers, PBMs, pharmacies, physicians, or patients, have little to no visibility into any quality metrics for the manufacturers of drug products or the products themselves. A system of "quality scores" is proposed to enable health-systems and other purchasers and payers of medication to differentiate among drug products according to evidence-based metrics. Metrics influencing the quality scores described herein include both broadly applicable regulatory information and more drug-specific, third-party chemical analysis information. The aggregation of these metrics through a proposed set of rules results in numerical values on a 0–100 scale that may be further simplified into a red/yellow/green designation. The simplicity of such scores enables seamless integration into existing healthcare systems and an integration scheme is proposed. Using real-world data from currently on-market valsartan drug products, this proposed system generated a variety of quality scores for six major manufacturers. These scores were further evaluated according to their current market price showing no significant correlation between quality score and price. The implementation of drug quality scores at healthcare institutions in the United States and their potential utilization by regulators, could create a much-needed, market-driven incentive for pharmaceutical manufacturers to produce quality medications that would reduce drug shortages and improve public health.

This landmark paper is attached to this testimony and offers the first real blueprint of how independently generated, evidence-based drug quality scores can be built and utilized by healthcare systems throughout the U.S.

Regulatory Interventions

Finally, we believe there are a number of actions that the FDA and Congress could take that would bolster the effectiveness of the solutions above and further strengthen Federal oversight of drug quality.

First, the proposed industry-driven solutions of certified drugs and drug quality scores could be significantly strengthened by incentives or requirements put in place by government payers. For example, the Department of Defense (DoD), which purchases its own medications, could require independent certification prior to purchase

or provide incentives for manufacturers to do so. These concepts could also be included in legislation currently proposed to reform government purchasing of drugs (including for DoD) to incentivize sourcing from the U.S. and move pharmaceutical manufacturing to America.[72]

Second, legislation could fill critical voids in the FDA's current ability to enforce appropriate measures for ensuring the safety and quality of the Nation's drug supply. In the aforementioned Duke Margolis Center event, representatives from the FDA presented data from a survey of physicians. When asked, "Which, if any, of the following are functions of the FDA in terms of regulating drug quality?" the top answer was, "Remove a drug from market if unexpected risks are detected."[73] It is a sad irony that this is one power that the FDA does not have.

Congresswoman Rosa DeLauro (D–CT) has introduced H.R. 1108, the Recall Unsafe Drugs Act,[74] which would remedy this situation by providing the FDA with the authority it lacks to conduct the *mandatory* recalls of drugs. The bill was reintroduced in January 2020, along with a call from the Congresswoman to recall all ranitidine products.[75] Valisure strongly supports this legislation, which would mirror the mandatory recall authority FDA already has over medical devices, food, and biological products, but lacks for drugs.

Finally, another avenue where independent batch-level validation of drugs could easily be applied is drug importation. Drug importation is a unique opportunity to reimagine the drug supply chain and rebuild it in a way that helps ensure drug quality by incorporating independent chemical analysis of all imported products—essentially making all imported drugs certified drugs. We believe that drug importation is not only an important opportunity to provide lower-cost drugs to American consumers, but to enable even higher quality assurance than is presently possible in the current domestic drug supply.

In general, Valisure supports the framework set forth in the administration's Importation of Prescription Drugs Proposed Rule, particularly the proposed batch-level testing of all imported products. However, it is critical that the rule is revised to ensure that this testing is performed by independent laboratories rather than requiring further cGMP testing conducted by manufacturers that would be subject to the same conflicts of interest and errors as under our current system.[76] (Attachment A)

Valisure is greatly honored by the engagement it has received from government agencies and legislators and is open to exploring any avenues in which it can help to increase quality assurance and transparency in medications.

COVID–19 AND THE IMPACT ON MEDICATION QUALITY

In addition to its devastating toll on global health and economies, the COVID–19 pandemic has had significant impacts on the drug supply chain. Although finding treatments and vaccines for the virus and caring for the sick are the immediate first-order problems to address, it is becoming increasingly clear that one of the biggest second-order issues will be serious disturbances to the U.S. pharmaceutical supply chain. Drug shortages are already affecting Americans prescribed medications being repurposed for COVID–19 treatment,[77] and the shutdown of overseas manufacturing will likely create dozens of widespread shortages in the months to come—many of which we have little visibility into today.

In addition to the challenge of drug shortages, existing pharmaceutical quality problems may be exacerbated by the COVID–19 crisis. Many safety and quality issues stem from overseas manufacturers cutting corners, and it is certainly possible that many more corners will be cut in the scramble to ramp back up production and fill backorders. The potential for the market to be flooded with counterfeit, substandard, and tainted products is a serious concern, particularly in light of the suspension of routine FDA inspections,[78] the approval of previously banned manufacturers, and dramatically increased demand for specific drugs.

Through Emergency Use Authorization Act (EUA) authority, the FDA has chosen to make decisions now for the good of public health that will undoubtedly impact public safety in the future. For example, in its efforts to authorize production of large quantities of several drugs, the FDA has lifted its ban on one overseas manufacturer, Ipca Laboratories. The FDA had previously banned products from three Ipca manufacturing facilities because of rampant data manipulation and what the FDA in a warning letter called a "cascade of failure" at its plant in Silvassa.[79] One potential solution could be a mandate that any drugs produced under an EUA should be independently tested and certified before entering the U.S. market.

We are also concerned about quality problems resulting from escalated production of products used to treat COVID–19. Many of these drugs are also used broadly for the treatment of other medical issues by non-COVID patients. In the race to produce large amounts of these drugs, quality may be sacrificed for quantity, thereby exposing a large population to substandard products. Further, when new COVID treatments, preventives, and vaccines are developed, manufacturers will face enormous pressure to produce large volumes quickly. Without careful regulatory oversight and independent analysis, this could result in quality problems from rushed manufacturing.

It is important to note that manufacturing problems that arise from the escalated production of drugs and a lack of FDA inspectors on the ground at foreign plants could produce a domino effect for years to come. The lifecycle of a drug in the supply chain is many years and it could be many more before significant and serious issues are found, let alone addressed.

CONCLUSION

Since Valisure's founding, our mission has been to bring quality assurance and increased transparency into the opaque world of the nearly $2 trillion global pharmaceutical industry. While we initially brought these benefits directly to patients through our online pharmacy, we are encouraged by the growing awareness of these problems by public and private stakeholders and increased opportunities for collaboration. By working together, we strongly believe that we can bring critically needed quality and transparency in medications to all Americans.

We are grateful to the Senate Finance Committee's commitment to ensuring the safety and quality of the U.S. drug supply chain and hope to continue working with you towards this critical goal.

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tecting Our Pharmaceutical Supply Chain From China Act; S. 3538, Strengthening America's Supply Chain and National Security Act; H.R. 6731, Securing America's Pharmaceutical Supply Chain Act; H.R. 6630, Securing America's Critical Minerals Supply Chain Act; and H.R. 4710, Pharmaceutical Independence Long-Term Readiness Reform Act.

[73] *https://healthpolicy.duke.edu/sites/default/files/atoms/files/pharmaceutical_quality_slides_final.pdf*

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[76] *See* Valisure's comments to the proposed rule, *Importation of Prescription Drugs Proposed Rule,* Docket No. FDA–2019–N–5711. *(https://www.regulations.gov/document?D=FDA-2019-N-5711-1247).* See Attachment A.

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ATTACHMENT A

Valisure

March 9, 2020
VIA ELECTRONIC FILING TO:
www.regulations.gov

Stephen M. Hahn, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Importation of Prescription Drugs Proposed Rule, Docket No. FDA–2019–N–5711

Dear Dr. Hahn,

On behalf of Valisure, the Nation's first and only analytical pharmacy, I appreciate the opportunity to comment on the FDA's proposed rule on the importation of prescription drugs. We commend the FDA's thoughtful approach to the rule, particularly the focus on batch-level testing of imported products. Drug importation is not only an important opportunity to provide lower-cost drugs for American consumers, but to enable even higher quality assurance than is presently possible with the domestic drug supply. We urge speedy implementation of the rule to allow States and stakeholders the opportunity to assemble Section 804 Implementation Programs (SIPs) as quickly as possible.

I. BACKGROUND ON VALISURE

Valisure is an online pharmacy attached to an analytical laboratory, and is the first and only pharmacy in America that chemically batch-validates every medication it sells at no additional cost to consumers. Founded in 2015, Valisure is headquartered at Yale Science Park in New Haven, Connecticut. Valisure is ISO–17025 accredited by the International Organization for Standardization (ISO) and is registered with the Drug Enforcement Administration (Pharmacy: FV7431137, Laboratory: RV0484814) and the FDA (FEI #: 3012063246).

Valisure's mission is to help ensure the safety, quality, and consistency of medications and supplements in the market. In response to rising concerns about counterfeit medications, the quality of generics, and overseas manufacturing, Valisure developed proprietary analytical technologies that it uses in addition to FDA standard assays to test every batch of every medication it dispenses. Valisure tests medications for correct dosage, major inactive ingredients, proper dissolution, and for the presence of carcinogens such as N-Nitrosodimethylamine (NDMA). Valisure cur-

rently rejects over 10 percent of medication batches based on these testing standards.

Over the past year, Valisure identified a fourth major carcinogen in valsartan and discovered the presence of NDMA in Zantac/ranitidine, which led to recalls of the drug throughout the United States and the world. Most recently, Valisure detected high levels of NDMA in specific lots of the drug metformin.

In an August 7, 2018 inspection of Valisure's facilities by the FDA, the FDA determined that since Valisure's unique testing facility is not a part of the pharmaceutical manufacturing system and does not perform release testing, stability testing, or any related services for pharmaceutical manufacturers, Valisure did not require FDA registration. However, Valisure has elected to maintain voluntary registration status with the FDA. Valisure also received guidance that since it operates outside of the manufacturing industry using the appropriate ISO guidelines as opposed to Good Manufacturing Practices (GMPs), any product failures or concerns that Valisure identifies should be reported back to the pharmaceutical industry. Valisure has complied with this guidance and regularly provides reports to applicable parties in the pharmaceutical industry.

II. COMMENTS ON THE PROPOSED RULE

Valisure supports the importation framework proposed by the rule. In particular, we support the rule's proposed batch-level testing of all imported products, which will help ensure the integrity and safety of the medication. Below, we offer specific comments on several key provisions of the rule, including suggestions to help ensure that importation can be done both efficiently and cost-effectively.

A. SIP Sponsors

Valisure supports the proposal to allow pharmacies and wholesalers to co-sponsor SIPs. Pharmacies, in particular, have significant expertise acquiring and distributing prescription drugs, as well as ensuring the quality of these products; this makes pharmacies uniquely well-suited to partner with State SIP sponsors. We also believe that a pharmacy could safely serve as both a co-sponsor and an Importer within an SIP. To help safeguard these arrangements, we recommend requiring States to establish sufficient oversight mechanisms to ensure that this dual role does not present a conflict of interest.

Valisure also supports the proposal to allow pharmacies and wholesalers to sponsor a SIP independent of a State ("Option 2" under § 251.2). We recommend limiting this option to pharmacies that can demonstrate the ability to manage the administrative aspects of the program, develop sustainable partnerships with reputable Foreign Sellers, and administer the required Statutory Testing with high-quality independent laboratories.

Finally, Valisure supports the proposal to allow pharmacies and wholesalers to serve as Importers, for all the reasons enumerated above. We agree that part of Importers' responsibilities should include an initial screening of imported products. In addition to a visual comparison of each product to the HPFB-approved drug, on-site laser spectroscopy-based techniques could be used to quickly screen products as a first-pass screening using handheld advices. This would require a relatively minimal investment by the Importer, but would add an additional level of security. However, this would not replace the need for significantly more detailed analysis by a qualified laboratory.

B. Covered Products

Valisure believes that the rule's restrictions on covered products would still allow the importation of many commonly used medications that not only provide significant opportunities for price savings, but have already been subject to critical quality and safety issues (for example, valsartan, losartan, and metformin). The proposed Statutory Testing for imported products could result in even safer products than are currently available for sale in the United States.

In particular, Valisure supports the FDA's decision *not* to exclude modified-release drugs and narrow-therapeutic index drugs from the definition of covered products. These are precisely the types of products that Valisure often hears quality complaints about from doctors and patients. Batch-to-batch variation in drug dissolution and dosage in narrow-therapeutic index drugs can translate into significant adverse events and negatively impact patients' clinical outcomes. Valisure's testing has revealed substantial quality and safety issues with many of these products: for example, products with significantly different dissolution rates across batches, and

batches of narrow-therapeutic drugs, like anticonvulsants, that fall outside the manufacturers' stated ranges. As noted above, we believe this rule is an opportunity to add an additional layer of testing that can actually improve the quality and safety of imported products versus the current domestic supply.

C. Statutory Testing

Valisure believes that the Statutory Testing is a critical component of the proposed rule that will help ensure that imported products are safe and high quality. In particular, Valisure supports batch-level testing of all imported drugs, which will provide an important safeguard that goes beyond the requirements for domestically marketed drugs. However, Valisure has several suggestions to ensure that this testing is additive and not redundant and is conducted by independent third-party laboratories.

a. Qualifying Laboratories

Valisure strongly agrees with the proposal that all qualifying laboratories should have an inspection history and must have satisfactorily addressed any objectionable conditions or practices identified during its most recent inspection. Valisure agrees that qualifying laboratories should be held to rigorous standards, namely ISO 17025 accreditation.

However, Valisure *disagrees* that qualifying laboratories should be required to hold Current Good Manufacturing Practice (CGMP) certification. CGMP laboratories, by definition, contract with pharmaceutical manufacturers. This raises a potential conflict of interest that could lead CGMP laboratories to compromise the integrity of their testing. Moreover, CGMP testing follows manufacturer specifications rather than scientific and physiological best practice. In the past year alone, academics and independent laboratories like Valisure have discovered serious drug quality issues that were missed by CGMP testing, including potent carcinogens found in losartan, valsartan, ranitidine, and metformin. In some cases, these carcinogens were found because FDA testing guidelines had not yet been updated; in other cases, carcinogen contamination was widespread but apparently missed during CGMP testing.[1] Regardless, these lapses have profound consequences for patient health.

In addition to raising a potential conflict of interest and possibly neglecting critical testing that is not prescribed by manufacturers, pharmaceutical companies placing their products for sale in the U.S. are already required to conduct a GMP analysis, making the testing in the proposed rule redundant in many cases. GMP testing is also particularly expensive; most contract research organizations (CROs) will charge more for a GMP test than a non-GMP test, even though the only substantive difference is the paperwork. As such, requiring qualifying laboratories to hold CGMP certification will unnecessarily raise the cost of the Statutory Testing and lower cost savings to American consumers.

ISO–17025 accreditation is rigorous, and actually goes beyond GMP by not only setting standards for laboratory and analytical methodology, but also governing quality systems company-wide including business practices. As such, Valisure urges the FDA to eliminate the requirement that qualifying laboratories hold CGMP certification in order to ensure that the sponsors of SIPs have the option of contracting with truly independent and unbiased laboratories.

b. Laboratory Testing Requirements

Valisure recognizes that 21 U.S.C. § 384 permits laboratory testing to be done by the Importer or by the manufacturer. However, Valisure remains concerned that permitting the testing to be conducted by the manufacturer significantly increases the risk of inadequate scrutiny (at best) and fraud (at worst). As discussed above, this is especially true if the testing is conducted by a CGMP laboratory that routinely contracts with the pharmaceutical industry or is itself owned or controlled by the manufacturer selling the product.

To lower the risk that manufacturer testing might allow low-quality products to be imported into the U.S., Valisure reiterates its recommendation that testing

[1] *See* VALISURE, *Valisure Citizen Petition,* June 19, 2019 (finding high levels of the carcinogen DMF in lots of valsartan); VALISURE, *Valisure Citizen Petition on Ranitidine,* Sept. 9, 2019 (finding extremely high levels of NDMA in ranitidine); VALISURE, *Request that the FDA recall of identified batches of metformin on the basis that, due to contamination with a probable human human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA,* March 2, 2020 (finding high levels of the carcinogen NDMA in lots of metformin).

should be permitted to be conducted by ISO-17025 certified labs rather than restricted only to labs that hold CGMP certification. This would allow SIP sponsors the option of requiring any imported products to be tested by independent laboratories free of potential conflicts of interest. Additionally, Valisure urges that the rule clarify that manufacturers cannot satisfy the Statutory Testing requirements through pre-existing release or conformance testing. To the extent products have already undergone release or conformance testing at a qualifying laboratory in the U.S., the FDA should stipulate that the Statutory Testing should be conducted at a separate, independent laboratory to ensure thorough analysis before the products enter the United States market. Valisure also strongly supports the requirement in the proposed § 251.16(e) that if testing is done by manufacturers, detailed data should be provided to the FDA.

D. Product Labeling

Finally, Valisure supports labeling imported products appropriately to allow pharmacists to be able to distinguish them on a shelf. However, Valisure suggests that the required language on each box include the stipulation that each product was batch-tested to help ensure safety and quality.

* * *

Valisure appreciates the opportunity to provide comments on the proposed rule and looks forward to working with the FDA and States to help implement the safe and affordable importation of drugs from Canada. If you have any questions or if we can provide any further information that would be useful, please do not hesitate to contact me at david.light@valisure.com or 833–497–7370.

Sincerely,
David Light
Founder and CEO
Valisure

ATTACHMENT B

EVIDENCE-BASED QUALITY SCORES FOR RATING DRUG PRODUCTS AND THEIR UTILITY IN HEALTH SYSTEMS

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ABSTRACT

The quality of drug products in the United States, which are largely produced overseas, has been a matter of growing concern.[1] Buyers and payers of pharmaceuticals, whether they are health-systems, insurers, PBMs, pharmacies, physicians, or patients, have little to no visibility into any quality metrics for the manufacturers of drug products or the products themselves. A system of "quality scores" is proposed to enable health-systems and other purchasers and payers of medication to differentiate among drug products according to evidence-based metrics. Metrics influencing the quality scores described herein include both broadly applicable regulatory information and more drug-specific, third-party chemical analysis information. The ag-

[1] Conti RM, Berndt ER, Kaygisiz NM, Shivdasani Y. "We Still Don't Know Who Makes This Drug," Health Affairs Blog, February 7, 2020. *(https://www.healthaffairs.org/do/10.1377/hblog20200203.83247/full/).*

gregation of these metrics through a proposed set of rules results in numerical values on a 0–100 scale that may be further simplified into a red/yellow/green designation. The simplicity of such scores enables seamless integration into existing healthcare systems and an integration scheme is proposed. Using real-world data from currently on-market valsartan drug products, this proposed system generated a variety of quality scores for six major manufacturers. These scores were further evaluated according to their current market price showing no significant correlation between quality score and price. The implementation of drug quality scores at healthcare institutions in the United States and their potential utilization by regulators, could create a much-needed, market-driven incentive for pharmaceutical manufacturers to produce quality medications that would reduce drug shortages and improve public health.

INTRODUCTION

As most of the United States' complex drug supply chain has moved overseas, especially to countries such as India and China, quality and safety concerns have become more pressing. Eighty percent of active pharmaceutical ingredients ("API") for products sold in the U.S. now come from outside the country, the vast majority from China.[2] As Dr. Janet Woodcock, Director of the Food and Drug Administration ("FDA") Center for Drug Evaluation and Research ("CDER"), has noted, this "use of foreign-sourced materials creates vulnerabilities in the U.S. drug supply."[3] Recent drug quality issues have threatened the health and safety of American consumers, including the widespread contamination of critical blood pressure medications,[4] gastroesophageal reflux disease drugs,[5] and diabetes medications[6] with carcinogens.[7] Not only do drug quality issues place patients' lives at risk, they also account for over 60 percent of drug shortages[8] and generate fear and mistrust that is an important cause of medication non-adherence.[9]

Certain manufacturers have exhibited substantive quality issues and even engaged in data manipulation. This issue is highlighted by the record $500 million fine imposed on the generics manufacturer, Ranbaxy, after it pleaded guilty to failing to report its drugs did not meet specifications. The firm also made false statements to the FDA. Ranbaxy knowingly manufactured drugs that tested out-of-specification, had unknown impurities, and would not maintain their expected shelf life.[10]

Although significant attention is given to overseas manufacturers, American companies are not immune from quality issues. Numerous cases exist of serious quality problems affecting American consumers caused by poor manufacturing practices at facilities in the United States.[11]

For these reasons, we applaud the FDA's recent recognition of the need for more transparency with regard to drug manufacturing.[12] Recalls and FDA investigations have made clear that not all manufacturers are alike in their capacity to reliably produce high-quality pharmaceutical products. However, purchasers of pharmaceutical products—including drug distributors, pharmacies, and health systems—

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[2] U.S.-China Economic and Security Review Commission, 2019 Report to Congress 250 (2019).

[3] Statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, "Safeguarding Pharmaceutical Supply Chains in a Global Economy" 2 (Oct. 30, 2019), *available at https://bit.ly/2SYjqqy.*

[4] *FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan). https://bit.ly/38MRM6C.*

[5] *FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)* (February, 27, 2020). *http://bit.ly/3b92dlP.*

[6] Reuters. (March 2, 2020). "Online Pharmacy Valisure Says Tests Show Carcinogen in Diabetes Drug Metformin." *The New York Times. (https://nyti.ms/2UhtwDw).*

[7] Edney A, Berfield S, Yu E. (September 12, 2019). "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S." *Bloomberg Businessweek. (https://bloom.bg/2x7P11z).*

[8] *See* Dr. Patrizia Cavazzoni, FDA, "The Importance of Pharmaceutical Quality" 11 (2020), *at https://bit.ly/37LwrJB.*

[9] Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. "Medication Adherence: Truth and Consequences." *Am J Med Sci.* 2016;351(4):387–399. doi:10.1016/j.amjms.2016.01.010. *(https://www.ncbi.nlm.nih.gov/pubmed/27079345).*

[10] White CM. "Generic Drugs Not as Safe as FDA Wants You to Believe." *Annals Pharmacotherapy* 2020;54(3):283–286. *(https://journals.sagepub.com/doi/full/10.1177/1060028019881692).*

[11] *FDA Updates on Multistate Outbreak of Burkholderia cepacia Infections."* (August 2, 2017). *(http://bit.ly/33pjhkK).*

[12] Woodcock J. FDA. *To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality—Not Just Medicine.* Oct. 24, 2019, *at https://bit.ly/2SOEy3P.*

often have no reliable way to distinguish between high- and low-quality manufacturers or their drug products.

The FDA's Task Force on Drug Shortages has endorsed the creation of a voluntary "rating system . . . to inform purchasers, group purchasing organizations (GPOs) for health care systems, and even consumers, about the quality management maturity of the facilities making the drugs."[13] This underscores the importance of the fundamental principle of having a quality score that can differentiate between manufacturers. However, since the FDA proposal is voluntary, it may not achieve broad implementation. Furthermore, it is important that the criteria used be evidence-based. Announcements have also been made by private industry for the creation of a commercially available drug quality scores platform intended for use by health systems.[14]

Any reliable rating system should draw upon objective, science-based, independently generated data that is not voluntarily provided by manufacturers but collected by independent parties. Although a quality score system may include voluntarily furnished data, it must be primarily based on independent data to be broadly applicable and thus optimally useful to healthcare systems. The American College of Cardiology stressed the need for "*independent* testing and verification of the chemical content of batches of pharmaceuticals" in a recent resolution[15] that emphasizes the necessity to rely on more than just the manufacturer's self-reported data.

These independent quality rating systems should be developed through a process that incorporates robust stakeholder feedback, including patients, providers, academic institutions, regulatory agencies and health systems. In order to spur such discussion and make meaningful progress towards establishing a viable system for use among an array of healthcare providers, the authors propose criteria for the creation of evidence-based quality scores, examples of use on existing drug products, and a mechanism for utilization exemplified by a proposed workflow for health systems.

METHODS

Quality Score Overview

Evidence collected in this proposed system originates from both broad manufacturer-level data and from specific product information. The combination of this data is intended to influence scores for specific drug products of a particular drug from a specific manufacturer. Although the evidence can be aggregated to evaluate a given manufacturer as a whole, the greatest utility to healthcare purchasers and payers is likely achieved by focusing on specific products. This is due to the immense complexity and opacity of the pharmaceutical supply chain. The source of ingredients used in any one drug product is considered proprietary and is therefore not easily accessible.

The specificity down to a drug product is not intended to directly describe a given National Drug Code ("NDC"), which further defines a drug product's dosage form and packaging. It is assumed that evidence gathered on a specific drug product will be applicable to all NDCs related to that drug product from the specific manufacturer, regardless of dosage level or packaging. As an illustrative example, if negative information is gathered for "manufacturer X's" valsartan 160mg tablets packaged in 100 count bottles, this will influence quality scores on NDCs for all valsartan tablets in all package sizes for manufacturer X. When substantially more data is available, future iterations of quality scores may directly describe individual NDCs or individual dosage forms.

The proposed system would generate a quality score on a numerical scale from 0 to 100, with 100 being the most desirable and highest achievable score and 0 being the lowest and least desirable score. Since all drug products legally sold in the United States are FDA-approved and produced at registered facilities certified as conforming to Current Good Manufacturing Practices ("CGMP"), the default assumption is that, absent evidence to the contrary, all products receive a default score of 100.

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[13] *Id.*

[14] Press release. (January 8, 2020). "Valisure and Govzilla Announce a Collaboration Focused on Creating a Platform for Evidence-Based Quality Scores for Drug Products." PR Newswire. *(https://prn.to/2xAuZgw).*

[15] American College of Cardiology resolution to the American Medical Association. (May, 9, 2019).

Criteria proposed herein are all based on information that is negative in nature and thus produces evidence for reducing a starting score of 100. Future iterations of such quality scores may also include criteria based on positive information that generates evidence for raising a score. The default value of such scores may be subsequently lowered to add opportunity for particularly well-performing manufacturers or products to outperform the default. It is also contemplated that temporal considerations be given to modify the impact of negative information and to eventually remove or significantly reduce its influence. The intention for a reliable quality score system would be to continuously incorporate new regulatory and chemical analysis data to enable optimal, real-time, guidance of drug product quality.

Quality Score Criteria

Proposed below are detailed criteria and their influence on a default score. These are based on independently gathered evidence from regulatory information and chemical analysis of on-market drug products obtained from a licensed pharmacy.

Category	Criteria	Qualifiers	Score Influence
Regulatory Information	**Warning Letter ratio to total inspections**	>1.5× 3-yr industry average >2× 3-yr industry average	−10 −30
	Form 483 ratio to total inspections	>10% 3-yr industry average >20% 3-yr industry average	−10 −30
	GMP related Consent Decree/CIA in place		−50
	Public Product Quality complaints	*e.g.,* % "bad odor" >2× competitors *e.g.,* % "bad odor" >4× competitors	−10 −30
	Serious adverse event	*e.g.,* % "death" >2× competitors *e.g.,* % "death" >4× competitors	−10 −30
Chemical Analysis	**Dosage failure**	Single batch >33% of batches All batches	−10 −30 −61
	Dissolution failure of USP	Single batch >33% of batches All batches	−10 −30 −61
	Dissolution failure of Physiological Conditions	>33% of batches All batches	−10 −30
	Carcinogen failure of FDA levels	Single batch >33% of batches	−30 −61
	Carcinogen failure at evidence-based, stricter levels	Single batch >33% of batches All batches	−10 −30 −61
	Heavy metals failure of FDA levels	Single batch >33% of batches	−30 −61
	Microbial detection failure by FDA method	Single batch >33% of batches	−30 −61
	Microbial detection failure by PCR method	Single batch >33% of batches All batches	−10 −30 −61

Category	Criteria	Qualifiers	Score Influence
	Ingredients ID failure, API	Single batch >33% of batches	−30 −61
	Ingredients ID failure, excipient	Single batch >33% of batches All batches	−10 −30 −61

Table 1. Proposed quality score criteria are categorized by information derived from regulatory data and chemical analysis data. For most criteria, the severity of negative influence on the score is dependent on qualifiers on the information gathered.

The specific criteria proposed above are primarily self-explanatory. Criteria requiring clarification are discussed below.

Form 483 and Warning Letter Ratio of Inspections—The 3-year average of total drug industry inspections, Form 483 letters and warning letters is aggregated and the ratios of Form 483 letters to total inspections and warning letters to total inspections is calculated. These same values are also calculated for an individual manufacturer and if the ratios for the manufacturer are higher than the global average by a set qualifier, a negative score influence is triggered. Future iterations may utilize total drug industry inspections within geographic regions as opposed to a global average. This could be an important refinement given the differences in inspection practices within the United States and overseas; such as domestic inspections are unannounced whereas foreign inspections often come with months of advanced warning.[16]

Public Product Quality Complaints or Serious Adverse Events—The ratio of this complaint or event to all others for this product is compared to other manufacturers of the same product. If the ratio for a concerning complaint or serious event is significantly higher than the average ratio of its competitors, a negative score influence is triggered.

Dissolution Failure of Physiological Conditions—This differs from dissolution failure of USP conditions for a variety of products where the registered USP monograph for dissolution testing does not conform to industry standard physiologically relevant conditions. For example, industry standard simulated gastric fluid is often used for 2 hours and has a pH of 1.2 and simulated intestinal fluid is often used for the remainder of dissolution testing thereafter and has a pH of 6.8. However, USP dissolution media for ibuprofen tablets prescribes using only one solution with a pH of 7.2 without any exposure to acid. Although testing ibuprofen tablets in USP solution may yield a passing test, performing dissolution testing in physiologically relevant media has been shown to yield certain specific products taking over 24 hours to dissolve whereas others dissolve quickly, as expected.[17]

Carcinogen Failure at Evidence-based, Stricter Levels—FDA regulations for acceptable daily exposures or intakes of various carcinogen compounds generally follow internationally accepted guidelines. However, there are cases where organizations such as the World Health Organization ("WHO") and the International Agency for Research on Cancer ("IARC") will provide guidance which differs from that listed by the FDA. This is currently the case with N,N-Dimethylformamide[18] ("DMF") which is classified by WHO and IARC as a Group 2A probable human carcinogen.[19] For the purposes of this proposed quality score system, a negative score influence is triggered when DMF levels exceed 96 nanogram but are less than 1,000 nanograms and a more severe negative score influence is triggered when DMF levels exceed 1,000 nanograms.

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[16] Government Accountability Office. (2019). "Preliminary Findings Indicate Persistent Challenges With FDA Foreign Inspections." *(https://www.gao.gov/assets/710/703077.pdf).*

[17] "Your Medication May Not Be Dissolving Properly." (2018). *The Valisure Notebook. http://bit.ly/38XVDNm* (accessed March 15, 2020).

[18] Light D, Kucera K. (June, 13, 2019). "Request that the FDA issue a regulation, revise industry guidance, and take such other actions." FDA Citizen Petition filed by Valisure, LLC. *(https://www.regulations.gov/docket?D=FDA-2019-P-2869).*

[19] International Agency for Research on Cancer and World Health Organization. *IARC Monographs on the Identification of Carcinogenic Hazards to Humans.* Volume 47, 71, 115 (2018). *(https://monographs.iarc.fr/list-of-classifications-volumes/).*

Category	Criteria	Qualifiers	Score Influence
Chemical Analysis	**Carcinogen failure: DMF >96 ng, <1,000ng**	>33% of batches All batches	−10 −30
	Carcinogen failure: DMF >1,000 ng	Single batch >33% of batches All batches	−10 −30 −61

Table 2. Quality score criteria definitions for "Carcinogen failure at evidence-based, stricter levels" specific for DMF.

Notably absent from the proposed quality score criteria is information regarding recalls. Although the existence of high volumes of recalls for a particular manufacturer of a drug product may intuitively induce a negative score influence, this may, in fact, be an indication of responsible quality surveillance. Furthermore, a lack of recalls may be indicative of overly lax quality assurance measures for a given manufacturer as opposed to a truly quality product. In the United States, drug product recalls are almost all voluntary and performed at the discretion of pharmaceutical manufacturers.[20] This conundrum warrants a deeper investigation. A retroactive review of chemical data compared with recall data could potentially better inform the correct view of product recalls. While such insights are yet to be elucidated, it was deemed best to leave such information out of the currently proposed quality score system.

Also absent from the quality score criteria is the FDA-proposed concept of quality management maturity. Indicators of quality management maturity have been proposed but appear to primarily rely on manufacturers' proprietary information.[21] To the authors' knowledge, there is no existing metric that uses publicly available inputs other than recalls which are discussed above. The lack of available information to assess the merits of quality management maturity for use in an independently derived and broadly applicable, evidence-based quality score system precludes it from inclusion in this proposal; however, future iterations may add such criteria when the information required for evaluation is made available or new indicators are elucidated.

It is envisioned that a drug quality score system or platform could include a mechanism for health system users to report potential drug quality issues, adverse events or send suspect medication samples for chemical analysis. This could create a much broader net to identify quality issues and if broadly utilized, such information could be valuable for the creation of new criteria to influence quality scores.

Quality Score Mechanics

To enable further ease of use and straightforward implementation within established healthcare systems, the proposed numerical quality score output can be categorized in a red/yellow/green fashion according to the following table:

Color Designation	Quality Score Range
Green	80–100
Yellow	40–79
Red	0–39

Table 3. Quality scores receive a color designation dependent on their numerical value.

Recognizing that a drug product receiving a red designation could induce significant impact within a healthcare system; special consideration was given to criteria which can trigger a red. In this proposal, only the quality score criteria within the category of Chemical Analysis is allowed to trigger a red designation. Even if the

[20] Newkirk M, Berfield S. (December 13, 2019). "The FDA Drug Recall System Is Voluntary, Haphazard, and Broken." *Bloomberg Businessweek. (https://www.bloomberg.com/graphics/2019-voluntary-drug-recalls-zantac/).*

[21] ISPE Drug Shortages Prevention Plan. (October 2014). *http://www.ispe.org/DrugShortagesPreventionPlan.*

sum of Regulatory Information criteria resulted in a score influence of −61 or below, the reported quality score would be a minimum of 40, yielding a yellow designation. The logic for this is rooted in the assumption that regulatory findings and public reporting can be influenced by many factors and do not have a well-established correlation to product quality, which is defined by its chemical composition. Supporting this is an excerpt from a 2015 White Paper from the FDA Office of Pharmaceutical Quality:[22]

> FDA has only limited information about the current state of pharmaceutical quality. FDA has no formal means for quality surveillance, except through inspections. . . . Furthermore, inspection findings have not been a reliable predictor of the state of quality.

Proposed Implementation for Health Systems

The intended use of the proposed quality scores system in an established healthcare system would be to inform and enable pharmacy procurement teams so that decision trees could be enacted. Decision trees could be implemented through healthcare IT systems that standalone or are integrated into the health systems' existing vender or purchasing system. A proposal of a decision tree utilizing such quality scores in order to purchase primarily green, occasionally yellow after manager review and completely avoid red is proposed for a health system where a robust process exists for managing drug shortages. Such drug shortage processes may include identification of substitute products, determination of alternative drugs or treatments and other remedies for mitigating or minimizing the impact of a drug shortage. In extreme cases that are reviewed by management, a poorly scoring medication product where there is no alternative could be treated by the health system as a drug shortage instead of purchasing a product designated red. Depending on the healthcare system, it may require a different decision tree and may elect to utilize different criteria, or adopt the same criteria with different degrees of influence on the quality score values.

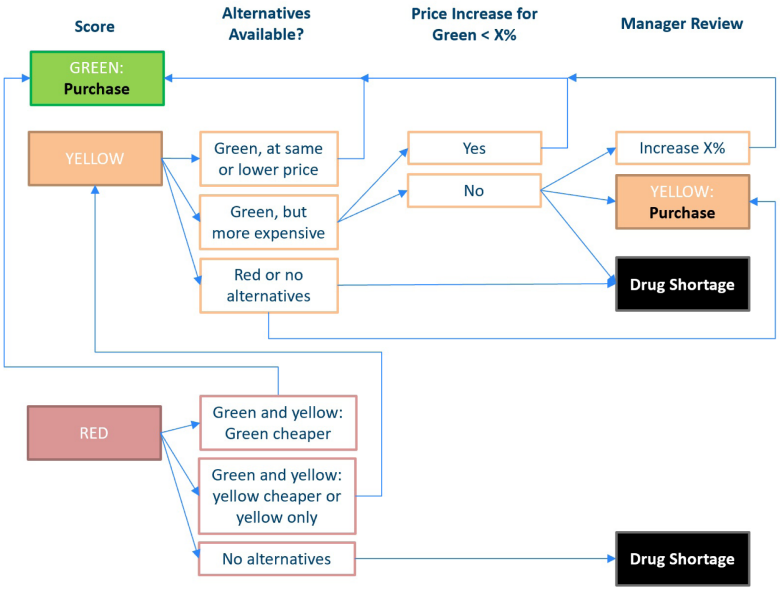

Figure 1. Proposed decision tree implementing red/yellow/green quality score designations. The first column describes the color designation of a drug product that is the default selection for the health system, which then triggers the decision tree.

[22] Food and Drug Administration. (2015). "FDA Pharmaceutical Quality Oversight: One Quality Voice." *(https://www.fda.gov/media/91721/download).*

RESULTS

The angiotensin receptor blocker drug, valsartan, has been subject to heavy scrutiny over quality due to a multitude of recalls after carcinogenic impurities were found.[23] This drug has been selected here for analysis using available data to generate a limited number of quality score criteria which give illustrative examples of how such quality scores can be derived. Regulatory information was gathered by Govzilla and chemical analysis information was acquired from Valisure's analytical laboratory that is attached to a licensed pharmacy.

Table 4A	Regulatory Information (2017–2020)						
	Inspections	Form 483	Warning Letter	Form 483 Ratio	Warning Letter Ratio	Form 483 % Above Global Ratio	Warning Letter % Above Global Ratio
Company A	38	20	0	0.526	0.000		
Company B	6	1	0	0.167	0.000		
Company C	36	24	1	0.667	0.028	26%	
Company D	15	9	1	0.600	0.067	13%	181%
Company E	10	3	0	0.300	0.000		
Company F	53	27	0	0.509	0.000		
Global 3-year	6,967	3,691	257	0.530	0.037		

Table 4B	Chemical Analysis						
	Batches Analyzed	DMF >96ng, <1000ng	DMF >1000ng	NDMA >96ng	Dosage	Dissolution	Ingredients
Company A	6	1	0	1	0	0	0
Company B	2	2	0	0	0	0	0
Company C	9	9	0	0	0	0	0
Company D	7	0	0	0	0	0	0
Company E	7	0	7	0	0	0	0
Company F	2	2	0	0	0	0	0

Table 4. Detailed regulatory information (Table 4A) and chemical analysis information (Table 4B) on available manufacturers of valsartan. Although the names have been deidentified, the data describes real manufacturers of valsartan drug products being currently sold in the United States.

Table 5	Quality Scores Impactful Criteria Findings (Score Influence)						
	Quality Score	% of Batches DMF >96, <1000ng	% of Batches DMF >1000ng	% of Batches NDMA >96ng	Form 483 >10%	Form 483 >20%	Warning Letters >1.5×
Company A	70			17% (−30)			

[23] *See* Food and Drug Administration, *Search List of Recalled Angiotensin II Receptor Blockers (ARBs) Including Valsartan, Losartan and Irbesartan. (http://bit.ly/3aUIbLF).*

Table 5	Quality Scores Impactful Criteria Findings (Score Influence)						
	Quality Score	% of Batches DMF >96, <1000ng	% of Batches DMF >1000ng	% of Batches NDMA >96ng	Form 483 >10%	Form 483 >20%	Warning Letters >1.5×
Company B	70	100% (−30)					
Company C	40	100% (−30)				26% (−30)	
Company D	80				13% (−10)		1.8× (−10)
Company E	39		100% (−61)				
Company F	70	100% (−30)					

Table 5. Data output for criteria triggering an influence on quality scores and the corresponding numerical influence on the scores denoted in parentheses, regarding current, on-market valsartan drug products from specific manufacturers. The final calculated quality scores are displayed and given their corresponding color designation.

Even with a drug such as valsartan that has had many quality issues, some of which appear to persist, the use of the proposed quality score system is able to identify a supplier that scores a green. Even among potentially mediocre product quality choices, those that appear to perform particularly poorly are identified by a red and can be reasonably avoided.

To further evaluate the impact on pricing by using the proposed quality score system, the relative costs of the valsartan drug products were analyzed across the six companies. Four dosage forms (40mg, 80mg, 160mg and 320mg) were evaluated using pricing from three different distributors and ensuring packaging size was consistent among all companies.

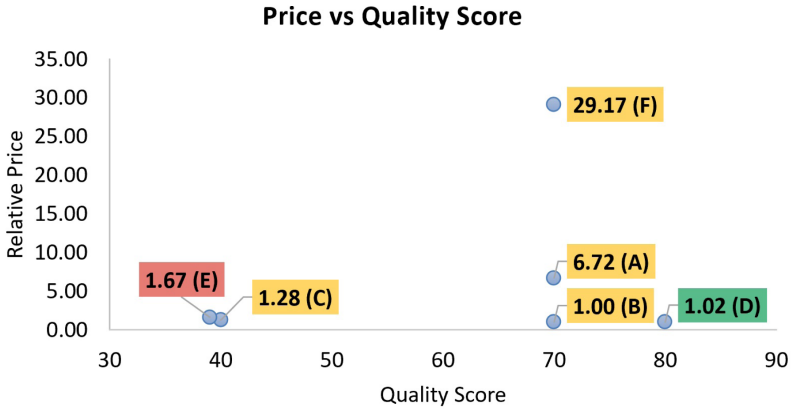

Figure 2. Relative pricing of drug products from companies A—F (denoted in parenthesis) plotted against their quality scores and given their respective red/yellow/green designation.

Although the decision tree in Figure 1 proposes the option of paying more for a higher scoring drug product, the pricing comparison illustrated above suggests that higher quality drug products do not necessarily cost more. Despite continued quality issues with valsartan, the least expensive option had the second-highest quality

score, the highest quality score option was only 2 percent more expensive and the lowest scoring option was 67 percent *more expensive.*

DISCUSSION AND CONCLUSION

When originally conceived, generic drug products were assumed to be equal in quality to each other and to the innovator product so the only differentiating feature would be the price paid. This has led to automatic generic substitution laws across the country where patients receive the generic selected by the pharmacy and this could change several times over the patient's course of therapy. The premise that every innovator and generic product is of equal quality is demonstrably false.[8]

With the changing market dynamics that drove pharmaceutical manufacturing offshore and made it very difficult to warrant acceptable quality, a new strategy is needed to ensure patient safety. The use of drugs that are improperly dosed as well as products that don't dissolve properly can put patients at risk of clinical failure or adverse events. The use of products with bacterial contamination, unacceptably high amounts of carcinogens or heavy metals may lead to unintended health problems as a result.[24]

We hope this will be a useful overview and baseline proposal for the use of quality scores for drug products. This is critical for adding much-needed transparency into the American drug supply chain and enabling health system purchasers and payers of medications to avoid low-quality drug products. As the data demonstrates with valsartan, high quality drug products do not necessarily cost more. Thus, even if a health system is unable or uninterested to add any additional purchasing cost or add any potential drug shortage burden, it is highly likely that the use of the proposed quality score system will provide a significant benefit in avoiding low-quality drug products.

Such action taken by established healthcare systems could help protect them from recalls and drug shortages while serving as a significant market driver to incentivize the manufacturing industry to produce quality products. Furthermore, the proposed quality score system could provide regulatory agencies with transparent and rational metrics with which to reward high-scoring manufacturers (*e.g.,* faster ANDA approvals) and/or penalize low-scoring manufacturers (*e.g.,* slower and more scrutinized drug approvals).

Overall, drug quality scores have the potential to improve public health; therefore, their continued development and implementation is highly encouraged.

ACKNOWLEDGEMENT

The authors would like to thank Michelle Call and Michael de la Torre from Govzilla, Martin Van Trieste from Civica Rx and Amber Jessop, Kaury Kucera and David Light from Valisure, for their assistance in providing data and expertise for this paper.

QUESTIONS SUBMITTED FOR THE RECORD TO DAVID LIGHT

QUESTIONS SUBMITTED BY HON. CHUCK GRASSLEY

Question. What is the role of new analytical technology in the evaluation of drug quality, and is there anything the FDA should be doing to ensure it incorporates the latest scientific best practices?

Answer. Apart from occasional improvements in efficiency, overall analytical technology for drug quality has remained largely unchanged over the past 5 decades. For example, analysis of well-studied carcinogenic impurities like N-Nitrosodimethylamine (NDMA) has been fairly consistent for roughly 50 years. Scientific studies describing the analysis of NDMA down to parts per billion and even parts

[24] Mathes RW et al. (2008). "Relationship between histamine2-receptor antagonist medications and risk of invasive breast cancer." *Cancer Epidemiology Biomarkers and Prevention,* a publication of the American Association for Cancer Research. Vol. 17(1): p. 67–72. *(https://www.ncbi.nlm.nih.gov/pubmed/18199712#).*

per trillion [1] were published as early as 1970, and Senate hearings [2] were held specifically about NDMA in medications in 1977. Even specific drugs like Zantac/ranitidine have been flagged by academics for many years for serious quality issues using standard scientific methods. Since Zantac/ranitidine's first approval in 1981, a Google Scholar search for "ranitidine NDMA" reveals over 500 scientific studies that reference this problem that took regulators 39 years to address, only after Valisure's independent analysis and drive for action brought global recalls.

The most critical "new" element of analysis that is having a dramatic impact today is analysis that is independent from the traditional pharma/regulatory world. At its essence, this means that the testing strives to independently answer the fundamental question of "is this a quality medication," as opposed to adhering only to a set of rules largely dictated by manufacturers that can have many limitations or biases. Whether it's using updated international standards, following scientific/academic best practices, or acquiring samples without significant bias, all these components summarized by the term "independent testing" have immense value and have already caught serious drug quality issues when they were otherwise missed or ignored. Most clearly illustrating this is the fact that every major drug that has had potentially life-threatening quality problems and recalls in the past 2 years (specifically, metformin, Zantac/ranitidine, nizatidine, valsartan, losartan and irbesartan) have all been flagged and tested by the FDA in their "Drug Sampling and Monitoring" program [3] since 2013 and all of these drugs have passed FDA testing. Many of these major drugs (metformin, Zantac/ranitidine, nizatidine) had serious issues that were first identified at Valisure.

In Valisure's opinion, FDA should work more closely with independent laboratories and academics to create a robust system of independent testing in addition to the prescribed industry and regulatory oversight currently in place. Such a collaboration would certainly help update FDA's methodologies to help safeguard the American public and our critical drug supply.

Question. From Valisure's perspective, what are the biggest gaps in the FDA's current regulatory oversight framework, and is there any current or proposed legislation to address these gaps?

Answer. One of the biggest gaps in FDA oversight is the agency's inability to conduct mandatory recalls of drugs. At a Duke Margolis Center event held in conjunction with the FDA in February 2020, representatives from the FDA presented data from a survey of physicians.[4] When asked, "Which, if any, of the following are functions of the FDA in terms of regulating drug quality," the top answer was "Remove a drug from market if unexpected risks are detected." It is likely that the American public would similarly be surprised by the fact that the FDA lacks the authority to force the removal of dangerous drugs from the market.

Valisure supports recent legislation introduced by Rep. DeLauro (D–CT) to provide the FDA with this critical mandatory recall authority,[5] which the agency already possesses over medical devices, food, and biological products.

Question. Does Valisure observe more quality issues from overseas manufacturers, specifically manufacturers in China and India, than from domestic manufacturers?

Answer. As most of the United States' complex drug supply chain has moved overseas, quality and safety concerns have become more pressing. Roughly 80 percent of the volume of active pharmaceutical ingredients (API) for products sold in the U.S. now come from outside the country, the majority from China.[6] This is an im-

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[1] Sen NP. (1970). "Gas-liquid chromatographic determination of dimethylnitrosamine as dimethylnitramine at picogram levels." *Journal of Chromatography.* Vol. 51, pp. 301–304. *(https://www.sciencedirect.com/science/article/abs/pii/S0021967301968682).*

[2] Senate hearings before the Subcommittee on Monopoly and Anticompetitive Activities of the Select Committee on Small Business on "Effect of Promotion and Advertising of Over-the-Counter Drugs on Competition, Small Business, and the Health and Welfare of the Public." June 1977. *(https://drive.google.com/file/d/1dTw6mwdMVFmoGAM1tQvHieohLiuzicgn/view).*

[3] Food and Drug Administration. "Drug Quality Sampling and Testing Programs." February 3, 2020. *(https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs).*

[4] Fisher A. (February 3, 2020). "Patient and Provider Perceptions of Pharmaceutical Quality." Food and Drug Administration, Duke Margolis Center for Health Policy. Page 64. *(https://healthpolicy.duke.edu/sites/default/files/atoms/files/pharmaceutical_quality_slides_final.pdf).*

[5] H.R. 1108, the Recall Unsafe Drugs Act (116th Congress).

[6] Edney A. "FDA Misled Senators on China's Role as Vital U.S. Drug Supplier." *Bloomberg News.* June 9, 2020. *(https://www.bloomberg.com/news/articles/2020-06-09/fda-misled-senators-on-china-s-role-as-key-u-s-drug-supplier).*

portant clarification from Dr. Throckmorton's oral statement during the hearing that "the U.S. provides about 28 percent, China about 13 percent" of API given that this "13 percent" figure references the percentage of registered facilities, not the volume produced at those facilities.

Although it is apparent we have a significant reliance on overseas drug manufacturers, the lack of transparency regarding where all the ingredients of a drug originate can make it difficult or almost impossible to determine country of origin for a specific drug product. The National Drug Code only tracks the final labeler of the drug and not the dose manufacturer, the producer of the API, or the producer of the fine chemicals that are used to manufacture the API. These labelers can also be re-packagers, adding another layer that keeps regulatory agencies and consumers from knowing the true provenance of the pharmaceuticals coming into the U.S. Furthermore, many manufacturers have multiple facilities around the world, and even though a final drug product may State that it was manufactured in a specific country, the reality is that this may not be an accurate representation.

In summary, due to the immense lack of transparency into origin of manufacturing, it is not currently possible for Valisure to determine which regions or specific manufacturers have the greatest incidence of quality issues. However, we do see widespread drug quality problems throughout this complex supply chain and believe more must be done to safeguard the hundreds of millions of Americans that rely on medications.

Question. On May 26, 2020, a consortium of leaders from eight health care institutions, including the Defense Health Agency, published a paper that advocates for an independently generated, evidence-based quality score system for drug products that could be used by private and public sector entities and regulators. Under this concept, what criteria would be used to determine the scores? What role does the FDA's proposed "quality management maturity" play in these scores?

Answer. The May 2020 paper[7] makes the argument that the criteria for determining drug quality scores should be science- and evidence-based and should be derived from independent sources and not only from manufacturers' reports. Results from independent chemical analysis of drug products could be combined with publicly available regulatory data and turned into simple red/yellow/green drug quality scores. Ideally, these scores would be continually updated with new regulatory and chemical analysis data to provide real-time, evidence-based guidance on drug product quality.

The FDA's "quality management maturity" ratings could theoretically be a useful input for drug quality scores, although this is difficult to gauge as the information and specific criteria is not currently available or finalized. Using only quality management maturity to generate drug scores would likely fall short of providing the science-based transparency into drug quality and safety that healthcare leaders are advocating for. Valisure strongly supports a collaborative approach between the FDA and healthcare industry stakeholders to finalize details of quality management maturity ratings and potentially incorporate them into drug quality scores.

QUESTIONS SUBMITTED BY HON. JOHN CORNYN

PHARMACEUTICAL PRODUCT TESTING

Question. Valisure conducts batch testing of every product that is dispensed. How does this process differ from the testing criteria FDA applies when they test pharmaceutical products? Would applying this standard to drugs with foreign sourced API prevent lower-quality, adulterated, or counterfeit medications from making it to the market?

Answer. Important background to this question is the fact that the FDA very rarely tests pharmaceutical products. Rather, the overwhelming majority of drug quality testing is conducted by the pharmaceutical manufacturers, who then self-report this data to the FDA. This presents a potential conflict of interest, as well as a significant opportunity for data manipulation and fraud, especially from foreign manufacturers where inspection processes differs from domestic manufacturers. In

[7] Dabestani A et al. (May 26, 2020). "Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems." *MedRxiv. (https://www.medrxiv.org/content/10.1101/2020.05.22.20110775v1).*

fact, of the over 4 billion prescriptions written in the U.S. annually, typically only a few dozen drug products are tested per year by the FDA.[8]

Valisure's testing follows a combination of FDA/industry guidance and adherence to scientific/academic best practice, which are not always perfectly aligned. The differences can be nuanced and complex, though essentially Valisure's testing strives to independently answer the fundamental question of "is this a quality medication" as opposed to adhering only to a set of analytical rules largely dictated by manufacturers that can have many limitations or biases. There are three primary components of Valisure's independent testing that occasionally differ from that of the FDA: criteria set by manufacturers, criteria set by regulators, and sourcing of samples.

Criteria for what to test for in a specific medication and how to test for it are usually determined by the manufacturer of that specific drug product. Testing for dissolution, or how a pill dissolves, is one example of methodologies registered by manufacturers that do not always follow scientific best practice and are not always indicative of conditions in a human body. For example, the registered testing condition for ibuprofen tablets uses a solution with a pH of 7.2 (water is pH of 7). The commonly accepted scientific standard conditions are to use "simulated gastric fluid" with a pH of 1.2 for 2 hours and then "simulated intestinal fluid" with a pH of 6.8, thereby simulating exposure to the stomach and intestines. Using this scientific standard protocol, Valisure identified batches of ibuprofen that do not dissolve for over 24 hours; however, when using the manufacturer-registered test, they dissolve in under 30 minutes.[9] Valisure uses the scientifically accepted dissolution conditions that represent the human body and therefore rejects some medication batches that are not able to dissolve in such an environment.

For criteria that is set by the FDA and not by drug manufacturers, like the limits for certain carcinogens, the agency does not always promptly incorporate independent scientific research, techniques, and guidance. For example, the carcinogen DMF (N,N-Dimethylformamide), is in the same "group 2A" carcinogenic risk class as NDMA (N-Nitrosodimethylamine) according to the World Health Organization (WHO). NDMA is the carcinogen responsible for recalls of major drug products over the last 2 years including blood pressure drugs valsartan, losartan and irbesartan, heartburn drugs ranitidine and nizatidine, and the diabetes drug metformin. Valisure filed an FDA Citizen Petition in June 2019 on the alarmingly high abundance of DMF in the drug valsartan.[10] The petition underscored that the WHO and International Agency for Research on Cancer (IARC) had reclassified DMF as a Group 2A carcinogen in 2018, but the FDA's last assessment was from 2017 when DMF was not yet considered at high risk of causing cancer in humans. Likely because of this outdated understanding, the FDA allows over 90,000 times more DMF to contaminate a medication than it allows for NDMA even though these two probable human carcinogens are now in the same, high-risk class. At Valisure, medications with excessively high DMF contamination (some have been found with over 1,000 times the current NDMA limit) are rejected even if they pass the FDA's current limit for DMF.

Lastly, the source of what is being tested can have a significant impact, even if the criteria are the same at the FDA and Valisure. The FDA will often request voluntary samples of a suspect medication direct from a manufacturer, which again presents a potential conflict of interest. At Valisure, we independently source the medication to minimize any potential bias. A critical example of this is the diabetes drug metformin where international regulators initiated recalls in December 2019 due to the presence of NDMA. On February 3, 2020, the FDA posted lab results from its testing of metformin from seven companies and 16 batches, finding that all passed the FDA's daily acceptable intake limit for NDMA.[11] However, Valisure independently acquired 38 batches of metformin from 22 companies through its phar-

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[8] Food and Drug Administration. "Drug Quality Sampling and Testing Programs." February 3, 2020. *(https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs).*

[9] "Your Medication May Not Be Dissolving Properly." (2018). *The Valisure Notebook. http://bit.ly/38XVDNm* (accessed June 22, 2020).

[10] Light D, Kucera K. Valisure FDA Citizen Petition on DMF. *Regulations.gov.* June 16, 2019. *(https://www.regulations.gov/docket?D=FDA-2019-P-2869).*

[11] Food and Drug Administration. Statement. "FDA posts laboratory testing results for NDMA levels in metformin." February 3, 2020. *(https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin).*

macy's distributors and found failures from 11 companies.[12] When the FDA acquired and tested samples provided by Valisure, the agency requested recalls from a number of these companies, including ones the FDA had previously passed.[13]

Whether it's using updated international standards, following scientific best practices, or acquiring samples without significant bias, all these components summarized by the term "independent testing" have immense value and have already identified serious drug quality issues that were otherwise missed. Illustrating this is the fact that every major drug that has had potentially life-threatening quality issues and recalls in the past 2 years (specifically metformin, Zantac/ranitidine, nizatidine, valsartan, losartan and irbesartan) have all been flagged and tested by the FDA in their "Drug Sampling and Monitoring" program since 2013 and *all of these drugs have passed FDA testing.*[14] These serious problems in metformin, Zantac/ranitidine, and nizatidine were first identified by Valisure.

Valisure strongly believes that independent batch-testing of all products, regardless of country of origin, would help safeguard against lower-quality, adulterated, or counterfeit medications from entering the U.S. market. Beginning with certain high-risk products, such as metformin, would be a good start that will already affect tens of millions of Americans, and can eventually be scaled to thousands of drug products. Creating a new category of "certified drugs" would inject much-needed transparency and security into the U.S. drug supply. Valisure is proof of concept that this testing can be done at no additional cost to consumers.

Regarding foreign-sourced API, it is important to note that when Dr. Throckmorton responded to Senator Cornyn's query about the percentage of active API for drugs in America sourced from China, his response that "the U.S. provides about 28 percent, China about 13 percent" does not paint the full picture. While China has 13 percent of the API facilities in the world, those are very large plants and supply roughly 60 percent or more of our API total volume.[15, 16, 17] The vast majority of the volume of our medications rely on foreign manufacturers, primarily China.

QUESTIONS SUBMITTED BY HON. TIM SCOTT

Question. We must do more to proactively address drug shortages and shortage risks, as well as to promote the production of medical products in the U.S. With that in mind, I recently released a proposal called the MADE in America Act, which would: (a) identify barriers to domestic manufacturing and recommendations for removing those barriers; (b) enhance efficiency and transparency when it comes to detecting and resolving drug shortages and shortage risks; and (c) create targeted tax credits for manufacturing critical medical products in Opportunity Zones. This proposal would also us to leverage incentives in a way that accelerates our economic recovery and bolsters our supply chain security at the same time.

For the two CEOs on Panel II, as we work to identify legislative and regulatory solutions, what do you see as some of the principal barriers to manufacturing medications domestically while keeping costs—and by extension consumer prices—low?

How does the United States' tax and regulatory environment for drug manufacturing and manufacturing more broadly compare with those of some of our competitors?

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[12] Light D, Kucera K, Wu Q. Valisure FDA Citizen Petition on Metformin. *Regulations.gov.* March 2, 2020. *https://www.regulations.gov/document?D=FDA-2020-P-0978-0001.*

[13] Food and Drug Administration. Update. "FDA names companies recalling ER metformin." June 11, 2020. *(https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin)*

[14] Food and Drug Administration. "Drug Quality Sampling and Testing Programs." February 3, 2020. *(https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs).*

[15] Edney A, Berfield S, Yu E. "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S." *Bloomberg Businessweek.* Sept. 12, 2019. *(https://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda).*

[16] Harper M. "Sanofi to start pharmaceutical ingredients company, which it says may avert future shortages." *STAT News.* Feb. 24, 2020. *(https://www.statnews.com/2020/02/24/sanofi-to-start-pharmaceutical-ingredients-company-which-it-says-may-avert-future-shortages/).*

[17] U.S.-China Economic and Security Review Commission, 2019 Report to Congress 248 (2019).

What types of job opportunities can domestic API, excipient, and finished drug form manufacturing and packaging create for lower-income and working-class Americans, along with middle-class Americans?

What do you see as the potential for advanced manufacturing technologies to accelerate drug development and bolster drug quality, as well as to address shortage risks? What are some of the hurdle's manufacturers are experiencing when looking to adopt technologies that could expedite production and improve drug quality, and how can Congress and the administration act to facilitate this type of innovation?

Answer. Valisure is not a manufacturer of drug products, nor do we provide any FDA-mandated Current Good Manufacturing Practice (cGMP) testing of drug products for pharmaceutical manufacturers. Valisure's core business is to analyze medications that have already been produced in order to screen out poor quality batches and manufacturers. By doing so, we help ensure that patients, doctors, and health systems can benefit from independently certified drugs. Given that the current regulatory framework for pharmaceutical manufacturing is largely dependent on the self-regulation of the pharmaceutical industry, including self-reporting of testing of manufacturers' own products, there is tremendous value to independent scientific analysis. This is particularly important given Senator Scott's concern about overseas manufacturing and the heavy reliance specifically on China, which supplies roughly 60 percent of the volume of active pharmaceutical ingredients (API) used in drugs sold in the U.S.[18]

Valisure is not an expert in the business considerations around drug manufacturing in the United States. However, Valisure supports incentivizing American pharmaceutical production of finished drugs, APIs, and the fine chemicals used to make APIs, especially for drugs that are considered essential for national security like antibiotics. Importantly, Valisure believes that independent analysis should be a part of the standard manufacturing process regardless of where a drug is made, and that any new legislation proposed for the production of medications in the U.S. should consider incorporating this critical safeguard.

QUESTIONS SUBMITTED BY HON. SHERROD BROWN

Question. Recent examples of adulterated products include the recalls of multiple drugs containing the API valsartan, and the over the counter drug known as ranitidine. Valsartan is found in several drugs that are used to treat high cholesterol and heart failure. The United States and 22 other countries issued a recall of valsartan after it was found to contain a cancer-causing chemical known as N-nitrosodimethylamine (NDMA). Because the FDA does not engage in the regular testing of imported products to check for quality and purity, regulators have been unable to ascertain how long this impurity has existed. Shortly after the valsartan recall, your company, Valisure, notified the FDA that it had detected NDMA in multiple batches of ranitidine in October 2019. Regulators are also unaware of how long we have been importing adulterated ranitidine.

Describe the process Valisure went through to notify the FDA of the adulterated ranitidine. Do you have recommendations to improve the process with which individuals are able to report suspected adulterations in products?

Answer. First, as additional background on valsartan, while the FDA very rarely tests drug products (only a few dozen tests are conducted a year out of the billions of bottles that are dispensed), valsartan was indeed tested by FDA in 2015 due to customer complaints, as was similarly contaminated losartan in 2013 and 2017, and irbesartan in 2017. Industry estimates suggest the contamination issue for valsartan began in 2011.[19] While the FDA reported that it tested multiple lots and manufacturers of valsartan and these other drugs, all the tested samples passed the FDA's testing standards.

Regarding ranitidine, Valisure presented extensive data to the FDA through an FDA Citizen Petition filed on September 13, 2019 on the inherent instability of the drug and its ability to easily form high amounts of the carcinogen N-Nitroso-

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[18] Edney A. "FDA Misled Senators on China's Role as Vital U.S. Drug Supplier." *Bloomberg News.* June 9, 2020. *(https://www.bloomberg.com/news/articles/2020-06-09/fda-misled-senators-on-china-s-role-as-key-u-s-drug-supplier).*

[19] Edney A, Berfield S, Yu E. "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S." *Bloomberg Businessweek,* Sept. 12, 2019. *(https://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda).*

dimethylamine (NDMA).[20] Apart from Citizen Petitions, Valisure is not aware of an effective mechanism for an independent laboratory like Valisure to raise drug quality or safety concerns to the agency.

Currently, there are two primary paths for a drug quality complaint to be filed. First, non-GMP (Good Manufacturing Practices) entities like Valisure can report an "adverse event" to manufacturers or the FDA, which are typically filed with thousands of individuals' complaints and generally receive very limited follow up, if any. Second, GMP entities registered with the FDA can make a GMP report of a quality violation to the FDA or the responsible manufacturer which triggers mandated follow ups and corrective actions.

Because Valisure does not itself manufacture products or conduct release testing for pharmaceutical companies, we are not a GMP laboratory. As such, following guidance from the FDA, Valisure submits dozens of drug quality problem findings directly to pharmaceutical companies. We believe these reports are most often ignored or filed away in the "adverse events" category which requires little to no follow-up. This means that many products that fail Valisure's testing are likely distributed to American consumers through other pharmacies.

To improve this process, FDA could issue guidance to industry that a report submitted to a pharmaceutical company from a "qualified laboratory" must go through a more rigorous follow-up process than are typically afforded the standard "adverse event" complaints. A "qualified laboratory" could be defined as one that has accreditation from an internationally recognized organization such as the International Organization for Standardization (ISO).

Question. Please describe the technology Valisure utilizes to test products before distribution. You mentioned in your testimony this service takes place at no cost to patients, and in your response to Chairman Grassley that it results in small additional costs. Please clarify what the cost of this service is, who pays for this testing, and what the financial impact on the patient is?

Answer. Valisure has developed proprietary, laser-based analytical technology that we use in combination with industry-standard approaches to analyze a variety of critical chemical components of medications. This includes analyzing for dosage/potency, dissolution (how a pill dissolves in a patient's body), identifying inactive ingredients, and detecting a range of impurities and carcinogens. Importantly, analytical technology specifically for the detection of well-studied carcinogenic impurities like NDMA has been largely unchanged over the past five decades.

Regarding costs, Valisure's optimized analytical workflows are themselves very cost-effective and the cost is amortized over large batches of a medication. This often translates to less than a penny per pill of additional quality assurance cost, which Valisure pays for from a portion of our retail pharmacy margin. As such, we are able to dispense medications at no additional cost to patients and still remain profitable.

If the Valisure model were to be expanded significantly—such as in the creation of what we term "certified drugs" in which independent analysis is performed at the same time as the FDA-required, standard analysis—the analysis would add minimal cost, which we believe could be borne by manufacturers without impacting patients. Health systems and government programs could help facilitate this concept by incentivizing or requiring independent analysis as part of their sourcing and bidding processes for drugs.

Question. What steps would you suggest Congress, regulators such as the FDA, and other organizations across the drug supply chain take to ascertain the extent of the purity problems that are possibly afflicting our supply chain, and address these problems?

Answer. To accurately ascertain the extent of drug quality problems in the U.S., Valisure recommends a broad analytical survey conducted by independent entities (in other words, entities operating outside the regulatory and pharmaceutical GMP system). Currently, the FDA conducts very limited surveillance testing (a few dozen products a year) of drug products based on perceived risks and customer com-

[20] Valisure FDA Citizen Petition Requesting Recall of Ranitidine and Other Actions. September 9, 2019. *Regulations.gov. (https://www.regulations.gov/docket?D=FDA-2019-P-4281).*

plaints.[21] Troublingly, this surveillance testing included each major drug that has had highly publicized drug recalls due to serious quality problems in recent years, including metformin, Zantac/ranitidine, nizatidine, valsartan, losartan and irbesartan, and all passed the FDA's testing. With this in mind, we believe that a properly funded survey of U.S. pharmaceutical products could be very impactful if conducted by qualified independent entities.

Regular, independent surveillance of drug quality is an approach that can be implemented immediately and is already being performed at Valisure on a small scale with tremendous impact. Such surveillance would likely identify specific quality issues, and the overall data it produces on all analyzed drug products could be used as guidance for buyers and payers in the form of drug quality scores. In a May 26, 2020 paper entitled "Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems," a consortium of leaders from eight health-care institutions proposed a system of drug quality scores to provide transparency into America's drug products.[22] These scores could be used by drug purchasers and payers to avoid low-quality products. Further, if used by regulators to incentivize or penalize manufacturers, these scores could be a powerful driver to produce high-quality pharmaceutical products.

A more definitive solution is what Valisure terms "certified drugs" that are independently chemically analyzed at the batch level and certified before being sold to a patient, pharmacy, wholesaler, or health care system. This added layer of quality assurance would improve public health and likely offer overall cost savings by mitigating drug recalls and increased hospitalizations that can arise from low-quality drugs. Such a system is very reasonable to quickly implement on a few high-volume and high-risk drugs, like metformin, and later scale up to many thousands of drug products. As a proof of principal, Valisure currently offers over 2,000 certified drug products in its pharmacy at no additional cost to patients.

Question. Are there other companies on the market that are able to do testing similar to what Valisure offers its customers?

Answer. There are many contract research laboratories in the U.S. that possess similar analytical capabilities as Valisure. However, most of these labs are GMP facilities and thus primarily, if not entirely, work for pharmaceutical manufacturers and follow very prescriptive analytical procedures that, like those performed at the FDA, have missed drug quality problems for decades. The largest source of independent analytical testing in the U.S. is in academia and universities. However, these analyses and research have historically been almost entirely ignored by regulators and the pharmaceutical industry as evidenced by hundreds of studies published in the past 4 decades on the carcinogenic and unstable nature of ranitidine. Valisure believes there is already very strong evidence and multiple examples that underscore the position that impactful improvements to safeguarding drug quality in the U.S. need to come from industry-led, independent analysis.

PREPARED STATEMENT OF MARTIN VANTRIESTE, RPH,
PRESIDENT AND CEO, CIVICA, INC.

Chairman Grassley, Ranking Member Wyden, and members of the committee, my name is Martin VanTrieste. I am the president and CEO of Civica, Inc. I am also a 35-year veteran of the pharmaceutical industry.

It is an honor to appear before you today, and an honor to follow a group of dedicated public servants. My dealings with the FDA and BARDA over the past few months have reminded me how tirelessly these officials work to serve the American people.

In my testimony today, I will:

- Introduce you to Civica and our non-profit model;
- Discuss several policy options to help the United States ensure a robust supply of drugs; and

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[21] Food and Drug Administration. "Drug Quality Sampling and Testing Programs." February 3, 2020. *(https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs).*

[22] Dabestani A et al. (May 26, 2020). "Evidence-Based Quality Scores for Rating Drug Products and Their Utility in Health Systems." *MedRxiv. (https://www.medrxiv.org/content/10.1101/2020.05.22.20110775v1).*

- Share some background on a recently announced agreement with the Federal Government to enhance U.S. manufacturing capacity for essential medicines.

ABOUT CIVICA

Civica is a non-profit 501(c)(4) social welfare organization established by U.S. health systems and philanthropies to reduce chronic drug shortages and ensure a safe and stable supply of essential medicines to U.S. patients.

That is our mission: to serve patients by making quality medications available and affordable.

Today, more than 50 health systems have joined Civica (Figure I). They represent approximately 1,200 hospitals and over 30 percent of all U.S. hospital beds. Civica also supplies the Veteran's Administration, the Department of Defense and "340B" hospitals, which care for vulnerable patients in some of the most underserved areas of the country.

FIGURE I.

The Supply Chain

Civica was primarily created to improve the resiliency of the supply of essential medicines used in hospitals daily, often for critical care. The drugs we make are not those with the highest return on investment. Rather, they are the ones that are identified and prioritized by our health systems—by doctors and pharmacists on the front lines—as the medications most important for high-quality patient care. Civica's members have also identified generic medications that are excessively priced, such as daptomycin, where Civica lowered significantly the market price.

Civica is implementing, simultaneously, a three-pronged product supply strategy to reduce chronic drug shortages and secure the supply of essential generic medicines for patients:

- Working with multiple generic drug manufacturers that have the U.S. Food and Drug Administration (FDA) approved manufacturing facilities and capacity to produce generic drugs under Civica's National Drug Code,[1] allowing manufacturers to re-enter the market or increase existing capacity. Civica is currently working with five supplier partners and is in negotiations with several more.
- Developing Abbreviated New Drug Applications[2] (ANDAs) to produce Civica medications using contract manufacturers.
- Building Civica manufacturing capability using Civica's ANDAs.

Civica is fully committed to stabilizing the supply of antibiotics, anesthetics, cardiac medications, pain management medications, and other essential sterile injectable medicines. To date, and in just over a year, Civica has launched 24 sterile injectable medications for use in hospitals across the country (see Table I). Civica is on track to deliver approximately 20 more medications in 2020, building toward 100 medications (in hundreds of dosage forms) by 2023.

[1] A unique numerical identifier indicating the labeler (manufacturer, repackager, or distributer), strength, and dosage form of each drug.
[2] The approval pathway for generic drugs.

Many of our drugs are used in the management of patients with COVID–19 (see Table I). And during this pandemic, Civica has contributed 1.6 million containers of medicine to the Strategic National Stockpile.

TABLE I. CURRENT CIVICA MEDICATIONS

Drug	Source of finished drug	API Source	COVID–19	Surge	SNS
Aminocaproic acid	USA	Japan			
Calcium chloride	USA	Germany			
Ceftriaxone	Portugal	Italy*			
Daptomycin	India	Hungary			
Dexamethasone	USA	France			
Diazepam	Italy	Italy			
Fentanyl	USA	USA	Y	5mL – 224%	
Glycopyrrolate	USA	Finland	Y		
Heparin	USA	USA	Y		
Hydralazine	USA	Japan			
Ketamine	Portugal	Germany	Y	5mL – 367% 10mL – 265%	Y
Labetalol	Portugal	Italy	Y		Y
Lidocaine	Portugal	Spain	Y		Y
Metoprolol	Portugal	Spain/India			
Midazolam	USA	Israel/India	Y	5mL – 324%	Y
Morphine	USA	USA	Y		
Naloxone	USA	USA			
Neostigmine	USA/India	Austria	Y		
Nicardipine	USA	Italy			
Ondansetron	USA	Spain/India			
Prochlorperazine	USA	Italy			
Sodium bicarbonate	USA	USA	Y		
Tranexamic acid	USA	Italy			
Vancomycin	Denmark/ USA	Denmark*	Y		Y

Source of finished drug refers to the country of manufacture of the sterile vial or prefilled syringe.
API Source refers to the country of origin of the active pharmaceutical ingredient.
COVID–19 identifies those drugs used in the management of patients with COVID–19, including management of patients on ventilators and treatment of secondary pneumonia.
Surge represents the increase in demand over anticipated volume for select drugs during the initial weeks of the COVID–19 pandemic. Note that some health systems had no increased demand; others ranged as high as 800 percent for select drugs. These data illustrate the ability of the "Civica model" to cope with a demand surge, but can't be used to extrapolate to national increase in demand or predict future demand.
SNS indicates that the initial set of identified drugs contributed to the Strategic National Stockpile.

*China is backup API source.

The Civica model brings together hospital systems and drug manufacturers to work collaboratively, ensuring both stable and fairly priced generic drugs for hospitals and predictable volumes for manufacturers. Key elements of the model include:

- Hospital systems join Civica, allowing them to purchase drugs in predetermined volumes at transparent and stable prices. Member health systems prioritize the medications needed to reduce shortages for patients and identify the volume requirements for their hospitals.
- Civica conveys this information to its manufacturing team or trusted manufacturing partners—those with a history of producing high-quality products. Manufacturers commit their production capacity based on long-term projected volumes of medications identified by the health systems.
- As a result, patient care improves as hospitals receive a reliable supply of the essential generic medications.

Because its specific mission is to create a robust, high-quality supply of essential medicines, several features of the Civica supply chain model may have lessons for the larger U.S. system, including:

- Long-term purchase take-or-pay commitments allow Civica, and our suppliers, to invest in quality systems;
- Use of backup suppliers and maintenance of a reserve stock averaging at least six months' supply;

- A preference to purchase medicines made in the U.S. where possible, followed by other highly regulated markets, followed by India and avoiding Chinese ingredients where possible in our drugs due to quality concerns; and
- Entrusting those on the front lines—hospital physicians and pharmacists—to prioritize the medications Civica makes, based on their experiences day-to-day or in times of crisis like the pandemic.

THE IMPORTANCE OF A ROBUST SUPPLY CHAIN

The global coronavirus pandemic has highlighted weaknesses in the U.S. supply chain for essential medicines and other medical supplies. Key products required to manage the epidemic have been unavailable or in short supply. Increased demand, both within the United States and among our trading partners, are important factors but have largely served to exacerbate supply chain shortcomings that are pre-existing and longstanding.

It is important to note that many of the medicines used to manage COVID–19, including the sedatives and neuromuscular blocking agents essential for patients on ventilators, were already in short supply prior to the pandemic. They represent a longstanding weakness in our supply chain that is explained, in part, by the relentless pursuit of ever-lower costs.

The desire for low-cost drugs—the race to the bottom in manufacturer pricing in order to get market share—is understandable, but it creates unintended consequences. Facing low margins and uncertain sales, companies are discouraged from investing in quality and incentivized to move production out of the U.S. to economies with lower labor costs, lower regulatory compliance costs and where they may receive direct or indirect support from foreign governments for to build new facilities.

Reliance on a sole source of supply, whether that is a single manufacturer or a supply from a single country, increases the risk of supply disruption. No purchaser should source essential drugs or other products from a single supplier.

Indeed, Civica's policy is not to supply all of any health system's needs for a given drug. If we were the sole supplier, we would be increasing rather than reducing vulnerabilities in the supply chain.

Longer supply chains and just-in-time inventory systems are especially vulnerable to disruption, whether due to quality problems or, as we've recently witnessed, export restrictions by foreign governments who understandably put their domestic needs ahead of those of their trading partners.

No single policy caused the exodus of pharmaceutical companies from the U.S., and it will take a multi-faceted approach—and a sustained commitment—to further diversify the supply chain and rebuild our domestic manufacturing capacity.

POLICY TOOLS

Nevertheless, the U.S. Government has a range of tools that can help rebuild capacity as well as protect against supply interruptions and keep the cost of medications in check. These include:

- Creating an essential medicines list to set priorities for investments, policy and regulatory reviews;
- Improving transparency in sourcing, pricing and drug quality;
- Utilizing incentives to encourage U.S. investment;
- Committing government programs to prioritize purchase of U.S.-made goods;
- Enhancing the Strategic National Stockpile;
- Directly supporting U.S. manufacturing; and
- Focusing on advanced manufacturing.

Target Essential Medicines

Civica selects medicines to manufacture based on the needs of patients, as prioritized by those on the front lines of the health care system. The U.S. government could benefit from a similar priority list to guide policy.

For these essential drugs, policymakers should incentivize contingency planning or redundant production lines for manufacturers to use in the event of a shortage, particularly for medicines that already have too few manufacturers.

To encourage investments in critical drugs, policymakers should consider waiving FDA user fees for drugs on the drug shortage list and when there is minimal competition.

Congress may also want to reconsider policies that turn generic drugs into sole-source products without competition. Specifically, the Drug Efficacy Study Implementation (DESI) program provides market exclusivity to companies in exchange for filing a New Drug Application on very old products. While intended to create an incentive for companies to submit efficacy and safety data to the FDA, this can result in unintended consequences, including reduced supply chain resiliency and dramatic price hikes.[3]

Transparency in Sourcing and Quality

Civica provides not only complete transparency on the source of its finished drugs, but also on the source of the active pharmaceutical ingredients (APIs) (Table I). But such transparency is not required by law. Any purchaser wishing to avoid active ingredients from high-risk countries is currently constrained by a lack of information. Congress could require country of origin labeling for both finished drug and API.

Similarly, Congress should consider steps to increase publicly available manufacturer quality information. It is a well-known quality principle that quality cannot be tested or inspected into a product. For example, if five tablets are tested from a batch of one million and they all pass, then all that is known is that those five tablets passed. In contrast, a mature quality system requires protocols, standard operating procedures, appropriate oversight and a culture of compliance. These are the ingredients of a quality system that are essential to producing quality pharmaceuticals. The supply chain itself must be considered a part of a quality assessment: A drug that does not reach patients cannot be considered high quality, whatever its other attributes.

There are tools that can be used to measure the maturity of a pharmaceutical quality system, such as those used for the Malcomb Baldrige National Quality Award and Parenteral Drug Association Quality System Maturity Model.

Making robust quality data available to health systems would help purchaser to take quality into account when buying medications. Congress could consider requiring the FDA to validate its quality metrics program[4] with a limited number of manufacturers within 1 year.

Manufacturers could be incentivized to participate. When the metrics have been sufficiently validated, manufacturer participation should be required.

We also commend Congress and the FDA for recently adding requirements for manufacturers to notify the FDA of discontinuance or interruption in active pharmaceutical ingredient supply and in the event of a demand surge or other factors that could interrupt supply.[5]

Tax Incentives

As a non-profit organization, Civica does not benefit directly from tax incentives to encourage U.S. manufacturing, but other manufacturers may, including some of our suppliers. For example, one recent proposal would allow 100 percent expensing for any new U.S. pharmaceutical manufacturing facility placed in service before 2026.[6]

Priority Purchase of U.S.-Made Goods

One change Congress could make, as proposed in recent legislation,[7] would be to amend the Trade Agreements Act of 1979 to clarify that pharmaceutical products would not be considered to have originated in a country if the API originated in a different country. Updating this definition would reverse a recent court decision, *Acetris Health, LLC v. United States,* that precludes U.S. government purchasers

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[3] Civica letter to Congress, February 6, 2020. *https://civicarx.org/letter-closing-loopholes-that-lead-to-unreasonable-price-increases-for-decades-old-drugs/*. Accessed May 24, 2020.

[4] Geok Yan Loo, U.S. Food and Drug Administration. *https://static1.squarespace.com/static/58d0113a3e00bef537b02b70/t/5e726c5316537f1aa5309d79/1584557142149/2P0410_Loo_CDERsApproach.pdf.* Accessed May 24, 2020.

[5] Food and Drug Administration Guidance for Industry: Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act (March 2020). *https://www.fda.gov/media/136486/download*.

[6] For example, S. 3537, the "Protecting Our Pharmaceutical Supply Chain from China Act of 2020," introduced by Senators Cotton, Blackburn, and Cruz.

[7] For example, S. 3538, "The Strengthening America's Supply Chain and National Security Act," introduced by Senators Rubio and Warren.

from giving preference, under the Buy American Act, to pharmaceutical products that originated entirely within the United States or our preferred trading partners.

Congress could also consider recognizing the real cost differences between U.S. drug production and manufacturing in low-wage countries, by increasing the incremental additional cost the government will pay in order to purchase U.S.-made goods from the current level of 6 percent.

Given that it will take time to rebuild U.S. manufacturing, it may be inadvisable to set a firm short-term deadline to exclude Chinese suppliers completely, but the government should have a goal of having at least one U.S. supplier for every U.S. essential drug, with annual targets and progress tracking.

Enhanced Strategic National Stockpile

The U.S. essential medicines list identified above can be used to guide an enhanced national stockpile. The Federal Government currently maintains an emergency stockpile of drugs and medical equipment in warehouses around the country. While some supplies are inexpensive and/or can effectively be warehoused for long periods, the cost of stockpiling more expensive products with limited shelf lives, such as drugs, could be reduced with a commercially managed "flow through" inventory so that drugs are distributed and used prior to expiry, with the stockpile being continually replenished with newer product.

Direct Government Support of U.S. Manufacturing

Recently, the Biomedical Advanced Research and Development Authority (BARDA) announced a new partnership that will help build more U.S. advanced manufacturing capacity for essential drugs.[8]

THE BARDA PARTNERSHIP

Under this agreement, BARDA will fund Phlow Corporation, a newly formed public-benefit pharmaceutical manufacturing company in Richmond, VA, to build a new state-of-the art continuous manufacturing facility to produce API.

On the same site, Civica will build a facility capable of producing finished sterile injectable medicines for U.S. patients on an ongoing basis and to meet the needs of the national stockpile. Civica will use API from Phlow and from Ampac Fine Chemicals, an API maker on the same site.

This partnership will create a 100 percent U.S.-owned and -operated end-to-end domestic drug manufacturing infrastructure to secure essential medicines and prevent shortages of these vital medicines in the future.

Advanced manufacturing

Advanced manufacturing is a term for newer technologies that will help improve the speed and flexibility of drug manufacturing. In the case of the BARDA agreement, Phlow will commercialize continuous manufacturing technology developed at Virginia Commonwealth University's College of Engineering. In contrast with traditional batch manufacturing, this approach offers several advantages, including:[9]

- Precise control of product quality;
- Ability to rapidly respond to changes in demand;
- Lower cost of production; and
- Reduced environmental impact.

As set forth in recent proposed legislation,[10] Congress could further support the development of advanced manufacturing by supporting the creation of Centers of Excellence and providing expedited review if a technology is likely to prevent or resolve a drug shortage, maintaining an adequate supply of critical medications for national emergencies, or promote the adoption of innovative approaches to drug product design and manufacturing.

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[8] Health and Human Services, May 19, 2020. *https://www.hhs.gov/about/news/2020/05/19/hhs-industry-partners-expand-us-based-pharmaceutical-manufacturing-covid-19-response.html.* Accessed May 24, 2020.

[9] Statement of Janet Woodcock, M.D., U.S. Food and Drug Administration, October 30, 2019. *https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Testimony-Woodcock-API_103019.pdf.* Accessed May 20, 2020.

[10] For example, S. 3532, the "Securing America's Medicine Cabinet Act of 2020," introduced by Senators Blackburn and Menendez, and S. 3780, the "Help Onshore Manufacturing Efficiencies for Drugs and Devices Act," introduced by Senator Peters.

Thank you again for your attention to this important topic. Civica looks forward to working with this committee as it considers how best to protect the interest of American patients.

QUESTIONS SUBMITTED FOR THE RECORD TO MARTIN VANTRIESTE, RPH

QUESTIONS SUBMITTED BY HON. JOHN CORNYN

Question. The COVID–19 pandemic has shown us that there are vulnerabilities in our supply chain. As demand has surged for medications for patients on ventilators, manufacturers have been unable to meet the needs. Your testimony outlines policy tools to better prepare against supply chain interruptions.

Can you expand on how we can incentivize production of essential medicines?

Answer. To incentivize production of essential medicines, the United States should first identify those drugs in order to guide policy and target incentives. Criteria could include: likely need in the event of a demand surge due to pandemic or other public health emergency; current U.S. sources of finished drug, API and, where relevant, key precursors; redundancy and resiliency of supply across the entire supply chain, U.S. and OUS, with particular attention to single- or geographically-concentrated sourcing. For these essential drugs, policymakers should incentivize contingency planning or redundant production lines for manufacturers to use in the event of a shortage, particularly for medicines that already have too few manufacturers. To encourage investments in critical drugs, policymakers should consider waiving FDA user fees for drugs on the drug shortage list and when there is minimal competition.

To incentivize U.S. manufacturing, Congress could consider allowing 100-percent expensing for any new U.S. pharmaceutical manufacturing facility placed in service before 2026 and waiving supplemental ANDA fees for manufacturers modifying an existing ANDA to create a new U.S. source of API or finished drug.

Congress could also ensure that the purchasing power of the U.S. Government is used to support a resilient drug supply chain, including sufficient U.S.-based manufacturing. For example, Congress could amend the Trade Agreements Act of 1979 to clarify that pharmaceutical products would not be considered to have originated in a country if the API originated in a different country, reversing *Acetris Health, LLC v. United States,* a recent decision that precludes U.S. Government purchasers from giving preference, under the Buy American Act, to pharmaceutical products that originated entirely within the United States or our preferred trading partners.

Congress could also increase the "Buy American" price differential from the current 6 percent to 20 percent to recognize the real cost differences between U.S. drug production and manufacturing in low-wage countries.

Congress could also consider requiring the FDA to provide expedited review if a technology is likely to prevent or resolve a drug shortage, maintain an adequate supply of critical medications for national emergencies, and/or promote the adoption of innovative approaches to drug product design and manufacturing.

Question. How can we reform the Drug Efficiency Study Implementation to allow for more manufacturers but also maintain incentives for manufacturers to go through the approval process for those "grandfathered" drugs?

Answer. The Drug Efficacy Study Implementation (DESI) program was begun by the U.S. Food and Drug Administration (FDA) in the 1960s after the Kefauver-Harris Amendment, to classify all pre-1962 drugs that were already on the market as either effective, ineffective, or needing further study. By 1984, final action had been completed on 3,443 products, of which 2,225 were found to be effective, 1,051 were found not effective, and 167 were pending.

In 2006, the FDA introduced the "Unapproved Drugs Initiative" with the aim of removing unapproved drugs from the market, including DESI drugs and new drugs that were marketed without FDA approval. The Initiative required NDA (New Drug Application) approval for DESI or "grandfathered" drugs. Once the FDA approves an NDA for a DESI drug, the existing unapproved drugs are removed from the market, until the pharmaceutical company obtains an ANDA (Abbreviated New Drug Application) approval from the FDA.

There are numerous benefits to NDA approval for DESI or "grandfathered" drugs. NDA approval demonstrates to physicians, health-care providers, and patients that

a drug is safe and effective. The Sponsor of an NDA must demonstrate how the entire end-to-end manufacturing process is reliable and reproducible, and consistently meets standards of identity, strength, quality and purity. This is particularly important for the prevention of drug shortages and ensures that patients receive quality products with greater certainty of safety and efficacy.

However, the exclusivity period awarded to the NDA sponsor and resulting lack of competition has resulted in substantial price increases to consumers, health systems and plans, including Medicare and Medicaid, and was associated with more frequent drug shortages. An analysis by Gupta et al. found that between 2006 and 2015, 34 previously unapproved prescription drugs were addressed by the UDI.

> Nearly 90 percent of those with a drug product that received FDA approval were supported by literature reviews or bioequivalence studies, not new clinical trial evidence. Among the 26 drugs with available pricing data, average wholesale price during the 2 years before and after voluntary approval or UDI action increased by a median of 37 percent (interquartile range (IQR) = 23% × 204%; P < 0.001). The number of drugs in shortage increased from 17 (50.0%) to 25 (73.5%) during the 2 years before and after, respectively (P = 0.046). The median shortage duration in the 2 years before and after voluntary approval or UDI action increased from 31 days (IQR = 0 − 339) to 217 days (IQR = 0 − 406; P = 0.053). (*J Manag Care Spec Pharm,* 2017, 23(10):1066–1076)

To reintroduce competition to the market following the end of the exclusivity period, generic manufacturers must invest substantial sums to bring their products through the ANDA development and approval process. While the NDA process benefits patients (as noted above), Congress could consider several avenues to promote competition and reduce the cost of this program to taxpayers:

- Allow FDA to end the exclusivity period if the NDA holder enters into business practices to create an artificial monopoly, like exclusive contracts with all viable API manufacturers or a restricted distribution channel (unless mandated by FDA) that prevents competitors from obtaining reference product.
- Require the NDA holder to provide reference product to potential competitors at no charge.
- Waive the ANDA fees for manufacturers of previously unapproved drugs seeking to re-enter the market and for new ANDA applicants.
- Require the NDA holder to submit confidential information to the government regarding its expenses to obtain an NDA approval, and terminate exclusivity if an analysis of Medicare spending data or national pricing and utilization patterns indicate that cost to the taxpayer has exceeded those expenses by more than a defined factor.
- Directly fund NDA development through an RFP process, allowing ANDA approvals to begin without any defined exclusivity period.

QUESTIONS SUBMITTED BY HON. TIM SCOTT

Question. We must do more to proactively address drug shortages and shortage risks, as well as to promote the production of medical products in the U.S. With that in mind, I recently released a proposal called the MADE in America Act, which would identify barriers to domestic manufacturing and recommendations for removing those barriers; enhance efficiency and transparency when it comes to detecting and resolving drug shortages and shortage risks; and create targeted tax credits for manufacturing critical medical products in Opportunity Zones. This proposal would also us to leverage incentives in a way that accelerates our economic recovery and bolsters our supply chain security at the same time.

As we work to identify legislative and regulatory solutions, what do you see as some of the principal barriers to manufacturing medications domestically while keeping costs—and by extension consumer prices—low?

Answer. Barriers to U.S. manufacturing include higher labor costs and additional regulatory costs, particularly associated with environmental and occupational health and safety approvals, in the United States compared with lower-cost economies.

Question. How does the United States' tax and regulatory environment for drug manufacturing and manufacturing more broadly compare with those of some of our competitors?

Answer. Civica is committed to manufacturing in the United States and, moreover, as a non-profit would not benefit directly from tax incentives (though some of our manufacturing partners might). Nevertheless, the examples of Ireland, Singapore, and, previously, Puerto Rico illustrate the potential of favorable tax treatment to attract pharmaceutical manufacturing.

Question. What types of job opportunities can domestic API, excipient, and finished drug form manufacturing and packaging create for lower-income and working-class Americans, along with middle-class Americans?

Answer. Pharmaceutical manufacturing creates direct employment for hundreds of thousands of Americans. These jobs include roles for chemical engineers, materials scientists, biological scientists, laboratory technicians, line operators, quality managers, compliance personnel, as well as all the associated ancillary management and support personnel. For example, the recently announced BARDA partnership with Phlow and Civica is expected to create hundreds of new jobs. Some of those will be filled by individuals with professional qualifications and experience in the industry, but others will be filled by training and growth opportunities within the local workforce.

Question. What do you see as the potential for advanced manufacturing technologies to accelerate drug development and bolster drug quality, as well as to address shortage risks? What are some of the hurdles manufacturers are experiencing when looking to adopt technologies that could expedite production and improve drug quality, and how can Congress and the administration act to facilitate this type of innovation?

Answer. Compared with traditional batch manufacturing, advanced pharmaceutical manufacturing has the potential to reduce production costs, improve flexibility and speed of production and reduce waste. As a more nimble manufacturing process, continuous manufacturing will help mitigate drug shortages caused by lack of access to API. Hurdles to advanced manufacturing include the cost of new capital investment and the regulatory cost associated with modifying the supply chain for currently approved drugs. In the generic market, these costs may be prohibitive, and companies are unlikely to invest to change the production of existing drugs without substantial support. To facilitate this type of innovation, Congress and the administration may wish to consider lowering the costs of new investments in U.S.-based advanced pharmaceutical manufacturing through tax incentives, direct grants or contracts; by waiving the FDA user fees associated with new or supplemental drug applications that use advanced manufacturing technology, and by supporting innovation and workforce development through the establishment of academic centers of excellence, provided they are directly and closely associated with commercial manufacturing enterprises. Congress and FDA should also evaluate the potential of system-based regulatory oversight that enables simpler and faster regulatory approval for manufacturing provided appropriate quality systems and protocols are in place.

QUESTIONS SUBMITTED BY HON. BENJAMIN L. CARDIN

Question. Prescription drug shortages have been a persistent and troubling occurrence. Many of the drugs in shortage are generic and have been off patent for years, which should lead to a market with reasonable prices and reliable manufacturing.

Instead, patients and providers in Maryland and nationwide struggle to afford and obtain many of these critical medications.

CivicaRx and its member hospitals look to address the issue of drug shortages by making their own generic drugs. I am excited that CivicaRx is focusing on generic drugs susceptible to shortages, and am curious to learn more about your company's drug shortage prevention practices.

How are the drug shortage prevention practices of CivicaRx different from those of other drug companies?

Answer. Civica differs from other drug companies in several important ways. First, Civica is a non-profit, non-stock social welfare organization established by U.S. health systems and philanthropies for the express purpose of reducing chronic drug shortages and ensuring a safe and stable supply of essential medicines to U.S. patients at a fair price. The drugs Civica makes are not those with the highest return on investment. Rather, they are the ones that are identified and prioritized by our health systems—by doctors and pharmacists on the front lines—as the medica-

tions most important for high-quality patient care. Civica's members have also identified generic medications that are excessively priced, such as the antibiotic daptomycin, where Civica lowered significantly the market price.

Additionally, Civica's member health systems sign long-term "take-or-pay" purchase agreements that allow Civica, and its suppliers, to invest in quality systems. The organization establishes backup suppliers for all drugs and maintains a physical reserve stock averaging at least 6 months' supply. This contrasts with a more typical 30-day supply distributed across the entire supply chain. Civica also sources medicines made in the U.S. where possible, followed by other highly regulated markets, followed by India, and avoiding Chinese ingredients where possible in our drugs due to quality concerns.

Question. Based on your experience, what recommendations for FDA, or Congress, would you suggest to better prevent drug and medical supply shortages?

Answer. To better prevent drug shortages, the FDA and/or Congress should give consideration to creating an essential medicines list to set priorities for investments, policy, and regulatory reviews. An essential medicines list can be used to guide policy and target incentives. For these drugs, policymakers could incentivize contingency planning or redundant production lines for manufacturers to use in the event of a shortage, particularly for medicines that already have too few manufacturers. To encourage investments in critical drugs, policymakers could also consider waiving FDA user fees for drugs on the drug shortage list and when there is minimal competition.

Improved transparency in sourcing and quality can better enable purchasers to choose products that are less likely to experience supply interruptions. To achieve this, Congress could consider country of origin labeling for both finished drug and API. In addition, increasing publicly available manufacturer quality information could be supported by establishing a timeline for FDA to finalize its quality metrics program and requiring manufacturer participation by date certain and/or incentives for manufacturers to participate.

Congress could also consider directing major Federal purchasers to establish a goal of having at least one U.S. supplier for every U.S. essential drug, with annual targets and progress tracking that take into account market share and ability to scale up production on a defined timeline.

Question. In May, the administration announced a 4-year, $354-million contract with a newly formed company, Phlow, to produce both drug ingredients and generic medicines in the U.S. that are in short supply and used to treat COVID–19 patients. Phlow has partnered with CivicaRx, and plans to make medicines and ingredients at CivicaRx plants and will open its own facility in Virginia in 2021.

Based on recent press articles, Phlow is partnering with CivicaRx to ramp up domestic production of certain pharmaceutical ingredients and medications. Part of this strategy will include building manufacturing facilities.

How long will this take?

What drugs is Phlow manufacturing?

I understand that Phlow is working with CivicaRx's existing contractors, but as I understand it none of the existing contractors are domestic. Can you elaborate on how you will build up domestic production?

Answer. A typical timeline for establishing a new pharmaceutical manufacturing facility, from the beginning of construction to commercialization, would be as soon as 36 months. That could be considerably shortened by expediting regulatory approvals. The timeline for Phlow to produce active pharmaceutical ingredient is shorter. In the meantime, Civica and Phlow are contributing to the strategic national stockpile through Civica's existing network of contract manufacturers, which prioritizes U.S. manufacturing where possible. Of the 26 drugs we've contracted to date, we manufacture 17 in the U.S. and 8 in Europe. The primary source of the API is in the United States or Europe for 21 of 26 products.

Civica and Phlow will create new U.S. capacity through the construction of new API and finished drug manufacturing facilities. In addition, the Phlow facility will manufacture key precursor compounds used to make APIs. These facilities will make drugs prioritized by the U.S. Government.

QUESTIONS SUBMITTED BY HON. SHERROD BROWN

Question. One of your policy recommendations to rebuild capacity and protect against supply chain interruptions is for the U.S. to establish an essential medicines list to set priorities for investments, policy and regulatory reviews.

Can you please elaborate on this policy recommendation? Which Federal agency would you suggest take the lead on developing this list? What considerations should be taken into account in building out this list of essential medicines?

What priorities should follow the development of an essential medicines list?

Answer. In establishing a list of essential medicines, the Secretary of Health and Human Services could draw on the expertise of multiple agencies. The U.S. Food and Drug Administration (FDA) has comprehensive information on approved drugs and their uses and countries of origin, as well as ongoing communication with sponsors and agency staff actively engaged in addressing drug shortages. The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) coordinates Federal efforts to enhance chemical, biological, radiological and nuclear threats (CBRN) and emerging infectious diseases (EID) preparedness from a medical countermeasure (MCM) perspective. The PHEMCE is led by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and includes three primary HHS internal agency partners: the Centers for Disease Control and Prevention (CDC), the FDA and the National Institutes of Health (NIH), as well as several interagency partners: the Department of Defense (DoD), the U.S. Department of Veterans Affairs (VA), the Department of Homeland Security (DHS), and the U.S. Department of Agriculture (USDA). The Strategic National Stockpile (SNS) is designed to supplement and resupply State and local public health agencies in the event of a national emergency anywhere and at any time within the United States or its territories. In 2018, oversight of the SNS was transferred to HHS/ASPR from HHS/CDC.

An essential medicines list should include drugs essential for routine clinical care. Civica relies on pharmacy and medical trends advisory committees from a cross section of U.S. health systems to identify the drugs most needed, and most vulnerable, on the front lines of care. A similar process may inform establishment of a U.S. list. Other factors for consideration should include a recent history of shortages, the number of suppliers in the market (including whether they, in turn, rely on common upstream suppliers of active ingredients), the potential for supply interruptions due to demand surges (such as during a pandemic or other public health emergency) and the likelihood of supply interruptions, taking into account geographical concentration of manufacture and country of origin, including the potential that supplies could be interrupted as other countries seek to ensure supply for their own populations or limit exports for strategic advantage.

PREPARED STATEMENT OF HON. RON WYDEN,
A U.S. SENATOR FROM OREGON

This afternoon the Finance Committee is holding its first meeting since March, focusing on the FDA's failure to adequately inspect foreign drug manufacturers for safety. In my view, the head of the FDA ought to face tough questions in any hearing on this topic. But FDA Commissioner Hahn is not with the committee today because the Trump administration blocked his testimony. They did this to prevent the committee from holding the FDA's point person accountable. I'd also asked for the committee to invite the journalist Katherine Eban here to testify, because she literally wrote the book on this issue. That did not happen either. In lieu of that, I'll ask consent to enter into the record testimony and articles from Ms. Eban on this subject.

While the committee meets for this hearing, COVID–19 is ripping through nursing homes and killing thousands of Americans every week. Unemployment is at near-Depression levels. The kindling laid down over centuries of racial injustice was reignited by the murder of George Floyd. The President is agitating for more violence and more escalation. Our Nation is suffering.

The injustice driving peaceful protestors to the streets over the last few days is woven throughout society. Since the committee is dealing with health care in today's hearing, I'm going to start with an immediate piece of urgently needed health-care reform. COVID–19 has hit the African American community harder than virtually any other group of Americans, and the status quo is immoral.

There is a long and terrible history of our health-care system working against black people in this country, from simply not listening when they report symptoms right up to performing cruel experiments on black human beings. That's part of why COVID–19 is having such an outsized impact on the African American community today. There's a risk that when a COVID–19 vaccine becomes available, vaccination rates in the African American community may be lower than elsewhere—because many in that community, for understandable reasons, do not believe that American health care is really looking out for them.

So I want to make something clear: this committee has muscle when it comes to health-care policy—$2 trillion in spending and jurisdiction over flagship programs like Medicare, Medicaid, the Affordable Care Act, and more. Today I'm calling on this committee to come together in the weeks and months ahead and use all that power to right the wrongs of the past.

As for the subject of this afternoon's hearing, I want to focus on one specific example of the FDA and the President teaming up to put Americans in danger. Let's talk about hydroxychloroquine.

Back in March, with the pandemic exploding nationwide, far-right media began talking about using this old malaria drug to treat COVID–19. The President glommed onto those reports, and without any valid evidence, he spent weeks declaring it the ultimate game-changer in the fight against the pandemic.

The FDA, in my view, bowed to the pressure and issued what's called an "emergency use authorization" for the drug. Doing so threw open the door to tens of millions of pills, including some, directly related to this hearing, manufactured inside facilities in Pakistan and India that have either failed FDA's inspection or never been inspected by the FDA at all. Studies have now shown that the drug has no benefit for COVID–19 patients. In fact, it is linked to higher rates of COVID–19 mortality.

Finally on April 24th, the FDA warned against using the drug in COVID–19 treatments, citing "serious and potentially life-threatening heart rhythm problems," but the FDA still says it can be imported from unapproved manufacturing facilities.

A recent article in *The New England Journal of Medicine* said the episode posed, quote, "fundamental threats to the U.S. drug evaluation process." Mr. Chairman, without objection, I'd like to have that article inserted into the hearing record.

The fact is, lots of Americans take this medication to treat other diseases, including lupus and rheumatoid arthritis. It's prescribed by their doctors, part of a valid treatment. They're counting on having a safe supply of their medication, and Donald Trump took that away from them. He repeated a bunch of far-right pundits touting junk science, and now the U.S. market is polluted with tens of millions of hydroxychloroquine doses that may or may not be safe. It's not clear there's a system in place to distinguish them from other stockpiles that came from approved sources. So if you're talking about FDA failures leading to greater risk for Americans, hydroxychloroquine is the case in point.

There's also the botched rollout of COVID–19 antibody tests. There's the emergency use authorization for faulty KN95 masks that pose a danger to health-care workers and first responders. There's the fact that the number of FDA inspections of foreign drug manufacturing facilities was already down under the Trump administration.

On this committee, there's bipartisan interest in seeing improvements at the FDA, and it makes sense to look for ways to build up our drug manufacturing capacity in the U.S. However, the Trump administration just handed a big contract for COVID–19 drug manufacturing to a company with no experience manufacturing drugs and no facilities in which to manufacture them.

That's not a good enough plan to help COVID–19 patients who are suffering right now. It also raises serious questions about how this administration would handle a COVID–19 vaccine, if and when a vaccine becomes available.

There's a lot to account for on this issue. It's unfortunate that the Trump administration is continuing to stonewall our oversight by blocking Commissioner Hahn from answering our questions today. Still, I thank our witnesses for joining us today, and I look forward to their testimony.

From: Katherine Eban
Author, *Bottle of Lies: The Inside Story of the Generic Drug Boom*
Vanity Fair Contributor

To: Senate Committee on Finance
Attn. Editorial and Document Section
Rm. SD–219
Dirksen Senate Office Bldg.
Washington, DC 20510–6200

Re: Statement for the Record
"COVID–19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process"

Date: June 1, 2020

Introduction

I spent a decade investigating the overseas manufacturing plants that supply a majority of generic drugs to the U.S. market, and the FDA's system for regulating those plants. That effort culminated in the publication of my *New York Times* bestselling book, *Bottle of Lies: The Inside Story of the Generic Drug Boom* (Ecco/Harper Collins, May 2019).

The book takes readers into the overseas manufacturing plants where the majority of our low-cost generic medicine is made. It reveals endemic fraud and dire conditions in an industry where companies routinely falsify data and circumvent principles of safe manufacturing to minimize cost and maximize profit. To report the book, I traveled to four continents, interviewed hundreds of sources and obtained over 20,000 pages of confidential FDA documents.

The U.S. drug supply is 90 percent generic, with a majority of those drugs coming from overseas, principally India and China. As well, 80 percent of the active ingredients in all our drugs, whether brand or generic, come from overseas, the bulk of those from China and India.

It is crucial to the health and safety of the American public that these drug products are effectively regulated. No substandard drug product should be permitted to enter the U.S. market. And yet, as my book uncovers, low-cost drug plants overseas routinely falsify their quality data in order to gain market approval. In a bid to cut costs and speed time to market, they use low-quality ingredients and take manufacturing shortcuts. The FDA, in numerous instances, has chosen to overlook these problems in its drive to approve a greater volume of low-cost medicine. The result is that generic drugs with toxic impurities, unapproved ingredients, dangerous particulates, or that are non-bioequivalent, have reached American patients.

The COVID–19 pandemic—which has increased drug shortages and snarled global supply chains—has intensified these problems. It has deepened our dependence on overseas drug manufacturers that produce low-quality medicine and has diminished the FDA's ability and inclination to police those manufacturers.[1]

After extensive reporting on this topic, it is my conclusion that: the FDA is not effectively regulating the overseas manufacturing plants that export to the U.S. market. The FDA is granting exceptions to these plants and allowing substandard drug products into the U.S. for reasons that include: concern over drug shortages; confusion about its own authority; reliance on drug companies' promises of reforms. The FDA's investigators are spread too thin, with depleted staff in overseas offices, anemic recruiting efforts, and a relatively small cadre of U.S.-based investigators willing to perform inspections overseas.

In conclusion, I believe the FDA must overhaul its foreign inspection system, more strictly enforce its own regulations, and create a transparent and verifiable system to ensure the integrity of our medicine and the safety of the American public.

1. The Widespread Problem of Data Fraud

Extensive data fraud at generic drug companies overseas first came to light in 2005, when a brave whistleblower, Dinesh Thakur, alerted the FDA to egregious fraud at India's largest drug company, Ranbaxy. In May 2013, after an 8-year investigation by the FDA, Ranbaxy pled guilty to seven felonies connected to its widespread fal-

[1] Katherine Eban, "The Coronavirus Pandemic Is Creating a Drug Supply Crisis Just When We Most Need Medicine," *Time Magazine,* March 26, 2020.

sification of quality data.[2] But Ranbaxy was hardly an outlier, as *Bottle of Lies* exposes. Dozens of overseas drug manufacturing plants have misrepresented their drug-quality data in order to gain market approval.

One FDA investigator Peter Baker, who I feature in my book, inspected 86 drug plants in India and China from 2012 to 2016, and found evidence of serious data-integrity violations in 67 of them. He uncovered this fraud and data manipulation by looking inside the computer systems of the manufacturing plants he inspected. There, he found widespread evidence that plants were engaged in hidden testing to pre-screen their drugs. This allowed them to figure out if the drugs would meet specifications, and then alter the parameters on the official tests which they showed to the FDA.[3]

Additional evidence supports the view that fraud and manipulation of quality data is endemic in overseas drug plants. In 2016, an investigation by China's own State Food and Drug Administration (SFDA) found that 80 percent of clinical trial data submitted by Chinese companies to regulators to gain approval for new drugs was fabricated.[4]

The generic drug industry has claimed that fraudulent practices have largely been corrected. But in October 2019, for an article in *STAT News,* co-author Sony Salzman and I analyzed the FDA's own records, which revealed that violations of data integrity are not only persistent and ongoing in overseas drug manufacturing plants, but are happening with greater frequency than in U.S. plants.[5] With the help of FDAzilla, a leading data analytics company, we analyzed 5½ years of FDA inspection records, from 2014 to 2019, for four major markets: China, India, Europe, and the United States.

The data showed significantly greater falsification or manipulation of manufacturing data in Indian and Chinese drug plants. For example, a January 2019 FDA inspection at Indoco Remedies in Goa, India, uncovered that the manufacturing plant had faked the data in its batch production records to justify the release to market of its diabetes drug glimepiride.[6] By contrast, the raw testing data showed that the drug did not meet quality standards and therefore should not have been released to patients.

While data integrity violations may sound minor and technical, for patients they can mean the difference between a safe, effective generic drug that functions just like the brand and a drug that is not equivalent to the brand, or that may contain toxic impurities or foreign particulate matter. In short, a difference between life and death.

2. Essential Difference Between U.S. and Foreign Inspections

In the United States, in order to inspect drug plants, FDA investigators simply show up unannounced and stay as long as is needed. But for overseas inspections—due to the complex logistics of getting visas and ensuring access to the plant—the FDA has chosen to announce its inspections in advance, despite there being no requirement to do so.

Overseas drug plants typically "invite" the FDA to inspect and the agency accepts. Plant officials serve as hosts to the visiting FDA investigators, who become their guests. It is not unusual for manufacturing plants to arrange local travel for FDA investigators. This system has allowed manufacturing plants to "stage" inspections, as one FDA investigator put it, and conceal evidence of data fabrication. Some companies have even sent in teams of data fabricators in advance of FDA inspections, to alter, shred, or backdate documents to create a facade of compliance.

This system of advance notification has also harmed the integrity and independence of FDA investigators. It has allowed companies to organize shopping trips, golf out-

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[2] Katherine Eban, "Dirty Medicine." *Fortune Magazine,* May 15, 2013. Available at: *https://fortune.com/2013/05/15/dirty-medicine/*.

[3] Eban, Katherine. "Americans Need Generic Drugs. But Can They Trust Them?" *The New York Times,* May 11, 2019.

[4] Fiona Macdonald, "80% of Data in Chinese Clinical Trials Have Been Fabricated," *Science Alert,* October 1, 2016, *https://www.sciencealert.com/80-of-the-data-in-chinese-clinical-trial-is-fabricated* (accessed September 30, 2018).

[5] Eban, Katherine, and Sony Salzman. "In Generic Drug Plants in China and India, Data Falsification Is Still a Problem." *STAT News,* October 29, 2019. *https://www.statnews.com/2019/10/29/data-falsification-still-problematic-china-india-generic-drug-plants/*.

[6] Food and Drug Administration. Warning Letter, Indoco Remedies Ltd., July 16, 2019.

ings, and tourist excursions for them, leaving them "captive and compromised," as a former head of the FDA's India office, Altaf Lal, described it.

In January 2014, with the FDA's permission, Lal launched what came to be known as the India pilot program.[7] He eliminated the months-long advance notice and company-arranged travel plans. Instead, the FDA gave only short notice—or no notice—of investigators' arrival for all inspections in India.

The FDA's new inspection program exposed widespread malfeasance that had previously been hidden. By showing up unannounced, the investigators uncovered an entire machinery that had existed for years: one dedicated not to producing perfect drugs, but to producing perfect results. The investigators found a bird infestation at one sterile manufacturing site. At another, they found a facility's paperwork for its sterility testing in perfect order, ensuring that the plant's air, water and surfaces were free of microbial contamination. Yet the samples didn't exist. They were testing nothing. The entire laboratory was a fake.

Under the India pilot program, the rate of inspections resulting in the FDA's most serious finding, Official Action Indicated, increased by almost 60 percent. The program succeeded in exposing endemic fraud and dire conditions in India's drug manufacturing plants. But in July 2015, the FDA abruptly ended the pilot program without explanation, and resumed pre-announced inspections. This raises the crucial question of how the FDA deals with the problems that it finds.

3. How the FDA Responds to Findings

It is striking that the FDA has all too frequently chosen to downgrade the findings of its own investigators.

In May 2017, in Linhai, China, an FDA investigator inspected Zhejiang Huahai Pharmaceuticals, the world's largest manufacturer of the active ingredient for valsartan, a generic version of the blood pressure drug Diovan. He found evidence at the plant that the company was failing to investigate potential impurities in its own drugs, which showed up as aberrant peaks in its test results. The investigator recommended the inspection be categorized as Official Action Indicated, which would have forced the manufacturing plant to urgently make changes or face further sanctions.

But in a September 7, 2017 memo, the agency downgraded the recommended classification to Voluntary Action Indicated, which allowed the company to make non-urgent corrections. The memo[8] concluded:

> The firm's response is mostly adequate including as it concerned the observation pertaining to their investigation of aberrant peaks on HPLC chromatograms. The firm provided data and information to demonstrate the peaks did not impact product and timeframes for improving their method and revising their investigation procedure.

In fact, the peaks were a clue to a compromised product. Less than a year later, the company wound up in the middle of a worldwide quality scandal. In July 2018, European regulators announced a harrowing discovery: the active ingredient made by Zhejiang Huahai contained a cancer-causing toxin known as NDMA.

The FDA's decision to overrule its own investigator and downgrade the Zhejiang Huahai inspection was not unique. According to the FDA's own data, which I obtained, from 2013 to 2018, out of 864 inspections in China of drug manufacturing plants that FDA investigators recommended as Official Action Indicated, FDA officials downgraded 78 of those. Of 1,514 inspections in India in the same time period, FDA officials downgraded 109. By contrast, in the same time period, out of 11,642 inspections that FDA investigators conducted in the U.S. and recommended as Official Action Indicated, only one inspection was downgraded.

These downgrades reflect the FDA's willingness to give foreign plants the opportunity to continue operations without sanctions.

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[7] Eban, Katherine. "Bottle X: Exposing Impurities in the Generic Drug Business." *Newsweek,* July 2, 2019.

[8] Tamara Felton Clark, Branch Chief, Global Compliance Branch 4, "Reclassification of Surveillance Inspection: VAI as Inspection Classification," CMS File—Work Activity 161861, Zheijiang Huahai Pharmaceutical.

4. COVID–19 Compromises

The coronavirus pandemic has intensified our dependence on potentially dangerous sources of foreign drugs, and the FDA's willingness to grant exceptions to source those drugs.

Most glaringly, in its efforts to source hydroxychloroquine, a treatment of unproven utility for COVID–19, in late March the FDA lifted restrictions on the Indian drug company Ipca Laboratories, which had previously been caught manipulating and deleting quality data, so that the U.S. could import the company's hydroxychloroquine sulphate and chloroquine phosphate active ingredients and hydroxychloroquine sulphate tablets.[9]

Even more concerning was the emergency use authorization the FDA issued on March 28th, which for the first time allowed the U.S. to import a version of chloroquine phosphate called Resochin, donated by Bayer AG, that had been made in plants in India and Pakistan that had never been registered with, or inspected by, the FDA.[10]

At the same time, the FDA has been forced to suspend foreign inspections, and is relying on information provided by drug companies, a number of which have previously been caught supplying falsified data.[11]

As well, plants that are facing regulatory restrictions, based on previous inspection findings of Official Action Indicated, are increasingly getting accelerated approvals to market their drugs, based on the Agency's regulatory discretion. The committee should request that data.

5. Suggested Reforms to Safeguard the U.S. Drug Supply

- **The FDA needs to overhaul its foreign drug inspection program**

The FDA's overseas offices are poorly staffed, and its cadre of U.S.-based investigators willing to perform inspections overseas is relatively small and demoralized. The FDA needs a specialized and highly trained workforce that can make a years-long commitment to serve overseas and become a "go to" group for emergency assignments. This would remedy the problem behind the FDA's anemic recruitment to foreign posts: a lack of clear career progression and promotion opportunities.

- **Unannounced inspections should be the norm**

The FDA's current regimen of pre-announced overseas inspections is counter-productive and ineffective, and allows companies to stage-manage inspections. Short notice, or no notice inspections, should be the norm.

- **Downgrades should be rare**

Too often, FDA officials at the agency's headquarters in Maryland overrule the judgment of investigators in the field, and downgrade recommended findings.

In the course of my reporting, an FDA spokesperson justified these downgrades as follows:

> The FDA can and does change assessments of a plant's compliance. After the initial data gathered by the investigator is reviewed by both the Office of Regulatory Affairs and the Center for Drug Evaluation, additional information can be taken into account. Oftentimes, a firm is not able to provide paperwork at the time of an inspection but can produce documents later on that provide more insight into the matter. Assessments can also change based on how willing a firm is to cooperate and fix issues that are found.

This system allows manufacturing plants to fabricate documents and generate excuses for submission to the FDA.

- **Drugs should be systematically tested**

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[9] Altstedter, Ari, and Anna Edney. "Censured Indian Plant Gets USFDA Nod to Supply Trump-Touted Drug." *Bloomberg,* March 23, 2020. *https://www.bloomberg.com/news/articles/2020-03-23/fda-lifts-import-curbs-on-maker-of-unproven-virus-drug-in-india.*

[10] Eban, Katherine. "Exclusive: FDA May Have Dropped Standards Too Far in Hunt for Chloroquine to Fight Coronavirus—Sources." Reuters, April 16, 2020. *https://www.reuters.com/article/us-health-coronavirus-bayer-chloroquine/exclusive-bayers-chloroquine-donation-to-u-s-raises-concern-about-fda-standards-in-pandemic-idUSKBN21Y2LO.*

[11] FDA Statement, "Coronavirus Disease 2019 (COVID–19) Update: Foreign Inspections." *https://bit.ly/3gL6O19,* March 10, 2020.

The FDA has largely used an honor system to verify the quality of drugs made overseas: it reviews data provided by the companies and conducts pre-announced inspections. Actual testing of drugs is rare.

The FDA should either institute a system of testing, or commission outside labs to do this testing, to serve as independent corroboration of quality.

- **Country-of-origin labeling on drugs and drug ingredients**

Consumers want to know where their drugs are made. There is no reason to conceal that information. The food we eat and the clothes we wear come with country-of-origin labeling. Yet when it comes to our prescription drugs, that information is deemed proprietary. It shouldn't be. Required country-of-origin labeling would likely underscore our dependence on foreign drug sources and accelerate the current push to return drug manufacturing to the United States.

- **Notify doctors of medication manufacturer switches**

Doctors are struggling to stabilize patients who are often being switched, month to month, between different manufacturers' versions of their monthly prescriptions. Those versions can vary widely in quality, absorption, and bio-availability. Doctors, particularly those that prescribe drugs where dosing is critical, should have the option to be notified about any medication switches that result in a change of manufacturers.

From *Time,* March 26, 2020

THE CORONAVIRUS PANDEMIC IS CREATING A DRUG SUPPLY CRISIS JUST WHEN WE MOST NEED MEDICINE

By Katherine Eban

As the world scrambles for a magic pharmaceutical bullet to stop the coronavirus, drugs perceived as cures—despite reed-thin evidence—have vanished from pharmacy shelves. Just last Friday, after President Trump touted the still unproven remedy of a malaria drug, hydroxychloroquine, the Food and Drug Administration lifted a restriction it had imposed on a Indian drug manufacturer with a record of manipulating its quality data, to allow it to make the active ingredient now suddenly in hot demand. With the United States long dependent on foreign drug manufacturers for low-cost medicine and key drug ingredients, it is little wonder that we have arrived at this frightening moment, with the FDA allowing companies that it didn't even trust enough last month to make any drug for the American public, to now churn out unproven drug ingredients for a largely untested off-label use.

Coronavirus has now done what years of U.S. Government Accountability Office (GAO) reports and congressional hearings could not achieve. It has laid bare the full perils of our dependence on an overseas drug supply. Not only has this pandemic intensified already serious drug shortages. But question marks loom over the safety of the drugs we are able to procure. Experts have long warned this day would come.

Last July, a Pentagon official testified before the U.S.-China Economic and Security Review Commission that U.S. dependence on Chinese-made prescription-drug ingredients constituted a national security threat. This was an understatement, even then. Over eighty percent of the manufacturing plants that make active ingredients for all U.S. drugs are located overseas, concentrated particularly in China. Furthermore, a majority of our finished generic drugs, which constitute ninety percent of the U.S. drug market, are made overseas, with a full forty percent coming from India, which in turn is also dependent on China for active drug ingredients.

Fast forward to the coronavirus pandemic, and that national security threat has turned into a full-blown national security disaster, with dangerous dominoes falling in the American drug supply, pointing to deeper trouble ahead.

India recently announced that it would curb the export of 26 drugs and drug ingredients, as it consolidates pharmaceutical supplies to treat its own population. The FDA announced, in light of travel bans, that it would halt all inspections at overseas drug plants. And the Chinese government recently threatened to impose restrictions on pharmaceutical exports to the U.S.

Even before the onset of coronavirus, serious questions loomed about the integrity of much of our low-cost foreign-made medicine. The FDA's foreign drug inspection program has been frighteningly threadbare for years: woefully understaffed and

poorly organized, with long-standing vacancies, as a December report by the GAO confirmed. But it also operates on an honor system, where the FDA gives foreign plants months of advance notice, does not systematically test drugs and instead, relies on reviewing company data.

This has allowed overseas plants to refine elaborate techniques for duping the FDA, a dangerous cat-and-mouse game that I first exposed in my book *Bottle of Lies: The Inside Story of the Generic Drug Boom.*

The overseas plants use hidden laboratories, secret testing machines, altered test results—and even clandestine drug samples taken from brand-name drug competitors—all to create pristine quality data to gain approvals from regulators and pass inspections. The result is that much of the quality data emanating from certain overseas plants is not "worth the paper it's written on," as one FDA investigator told me. Ipca Laboratories, the Indian drug company that just got the FDA's permission to make hydroxychloroquine, was found by FDA investigators to be manipulating and deleting quality data.

When the FDA announced it would suspend all foreign inspections, the FDA offered this to reassure the public: it would be "requesting records" from plants "in advance of or in lieu of" on-site drug inspections. In other words, the issue is not just the hydroxychloroquine made by one dubious company. Neither the FDA nor American consumers will have any idea whether the majority of our drugs on the market will be safe or work as intended, and will be relying entirely on information provided by drug companies, a number of which have previously been caught supplying falsified data.

Facing looming drug shortages, the U.S. finds itself at the mercy of China, which has threatened to cut active drug ingredients. India, which has already put an export hold on 26 vital drugs and drug ingredients. And Italy, another vital supplier of active drug ingredients, is under siege with almost 69,000 COVID–19 cases, and close to 7,000 deaths.

The generic drug market, responsible for ninety percent of the drugs Americans consume, operates on a "30/30/30 supply chain," said Martin VanTrieste, president of Civica Rx, a nonprofit drug maker aiming to ramp up U.S. manufacturing of generic drugs in short supply. At any given time, Trieste explained, there's a 30-day supply of active drug ingredients, a 30-day supply of drugs moving through the wholesale market and a 30-day supply of drugs on pharmacy shelves. That gives the U.S. government about "30 [days]" to avert major drug shortages. "My biggest fear is the shipping lanes close off," said Trieste, though it hasn't happened yet. "That would be setting off a disaster."

Within the last few weeks, lawmakers have introduced legislation that would incentivize innovation and advanced pharmaceutical manufacturing in the U.S., and require drug makers to more clearly disclose the origin of ingredients and the amount of stock on hand. The White House is pushing "Buy American" policies that would require the Federal government to prioritize the purchase of U.S.-made drugs and medical supplies.

But the flurry of proposals cannot make up for years of a broken drug supply, in which so many drug manufacturers looked for the cheapest way to make lifesaving drugs as far from vigilant regulators as possible. Facing a far-flung drug supply, the FDA failed to implement real verification systems—such as unannounced inspections and systematic drug testing—to safeguard the quality of foreign-made drugs. It was under this porous review system that millions of Americans wound up getting blood pressure medicine that contained a dangerous carcinogen.

If and when the COVID–19 pandemic subsides, our drug supply will require major reforms. The FDA must make unannounced inspections the norm for every plant it inspects, anywhere in the world. It must implement a system for routine testing of drugs. The big pharmacy chains, such as CVS and Walgreens, should also test the drugs they dispense.

And consumers should get country-of-origin labeling that discloses where their drugs and drug ingredients are actually made. That kind of information—available on our cereal boxes and clothing—is somehow deemed proprietary when it comes to lifesaving medications. These disclosures would probably shock most patients—and would go a long way to helping restore America's lost medicine manufacturing base.

In all likelihood, says VanTrieste, bringing drug manufacturing home will require an "all-out Manhattan project [style] initiative to get infrastructure back to the U.S. market." After all, it was just such a U.S. government effort—in the midst of World

War II—that led to one of the great breakthroughs in modern science, the commercial development of penicillin.

From Rueters, April 16, 2020

EXCLUSIVE: FDA MAY HAVE DROPPED STANDARDS TOO FAR IN HUNT FOR CHLOROQUINE TO FIGHT CORONAVIRUS—SOURCES

By Katherine Eban

On March 21, two days after President Donald Trump first touted chloroquine drugs as a "gamechanger" in the fight against COVID–19, administration officials privately described what they felt was a "win" in the president's efforts to build an emergency stockpile of the drugs: a hefty donation of pills from Bayer AG.

In an exchange of enthusiastic emails among federal health officials reviewed by Reuters, Keagan Lenihan, chief of staff of the U.S. Food and Drug Administration (FDA), cautioned that "3–4 days" of testing would be needed.

"Potentially serious issues with product so let's be careful when we take that win," she wrote.

Bayer has since donated three million tablets of the drug, called Resochin, to the U.S. national stockpile for treatment of COVID–19, the disease caused by the coronavirus. After a brief period of testing, its use in the United States was approved on an emergency basis.

But three U.S. government sources familiar with the matter told Reuters that there is reason to be concerned about the quality of Resochin and its makers, located in India and Pakistan.

Although some rules can be waived in an emergency, the FDA dropped its quality-control standards too far as it scoured the world for scarce supplies of chloroquine drugs, according to the sources, who spoke on condition of anonymity.

The plants that make Resochin ingredients and finished doses in India and Pakistan have never been registered with, or inspected by, the FDA, according to the three government sources, as well as FDA documents compiled in the private online database *FDAzilla.com.* Some chloroquine drugs were already approved by the FDA before the pandemic as antimalarial medications, a process that required plant inspections. Resochin was not approved.

Pakistani regulators, who inspected Bayer's Resochin plant in Karachi in 2015, found a "gross failure" in manufacturing processes there, according to documents from the Drugs Regulatory Authority of Pakistan, reviewed by Reuters. And though the FDA has never screened the Indore, India plant that supplies ingredients for Resochin, the U.S. agency has inspected other Indian plants run by the same Indian supplier and found serious deficiencies, including falsification of records, inspection documents spanning 2014 through 2019 show.

Responding to questions from Reuters about Resochin, FDA spokesman Michael Felberbaum said that the agency "sampled and tested the donated drugs to evaluate acceptability for importation" and they met appropriate standards.

Asked about Lenihan's March 21 email, the FDA spokesman said the agency "does not comment on alleged, leaked emails."

In a statement to Reuters, Bayer said that the FDA had tested Resochin "and found it to be of appropriate quality for release to the (stockpile) for emergency use. We are proud to make this donation to the U.S. government in the fight against COVID–19."

Resochin is part of a class of medications containing one of two active ingredients—chloroquine or hydroxychloroquine—that the Trump administration has praised as a potentially lifesaving treatment. But the effectiveness of chloroquine drugs against coronavirus has not been proven. Though in use for years in the United States as a treatment for malaria and autoimmune conditions such as lupus, the medicines can have serious side effects, including heart arrhythmias.

The three U.S. sources who spoke with Reuters, as well as an independent expert, said spot-testing is not always sufficient to ensure a drug's safety and effectiveness, and plant inspections normally done by the FDA are crucial to ensuring overall quality.

"If you're talking about millions of doses, you can't test every product," said Stephen Payne, who for years chaired a practice group specializing in the FDA and health care at a global law firm. "You have no idea what you don't know."

A PHOTO OPPORTUNITY

Trump first endorsed chloroquine drugs to treat COVID–19 from the White House podium on March 19, citing "very, very encouraging early results" and downplaying any risks. "If things don't go as planned, it's not going to kill anyone," he said.

The statements came as the administration was being hammered for its slow response to the growing coronavirus crisis, which to date has infected more than 637,000 people in the United States, killing almost 31,000. His comments set high public expectations for the drugs, which are now being snapped up all over the globe.

In emails two days later, federal health officials greeted the Bayer donation of chloroquine phosphate, or Resochin, with eagerness.

Cicely Waters, director of external affairs for the U.S. Department of Health and Human Services (HHS), saw a media opportunity. A shipment of two million tablets was due to arrive at John F. Kennedy International Airport in New York City.

"I would like to get photos of the product coming off of the FedEx plane so we can be prepared to support the story with visuals if this turns out the way we hope," wrote Waters.

Lenihan of the FDA told the group of health officials that "if it is the product we think it is and it is not toxic we will release it to ASPR"—the Assistant Secretary for Preparedness and Response, a division within HHS.

Reached by email, Lenihan referred Reuters back to the FDA press office. Waters did not respond to an email seeking comment.

One of the participants in the March 21 email discussion appeared to raise the issue of which agency should get credit for the deal. Joseph Hamel, ASPR's manager of strategic innovation and emerging technology, asked in an email to the group: "How do you want to handle? FDA win? ASPR win? Happy either way, please let us know."

Hamel did not return an email seeking comment.

Asked about the email exchanges, an HHS spokesman echoed the FDA's statement, saying the agency would not comment on "alleged, leaked emails."

"GROSS FAILURE"

The pills and ingredients welcomed by the administration had origins that should have raised red flags and prompted greater scrutiny, said the three sources who spoke to Reuters.

In 2015, Bayer's plant in Pakistan, Bayer Pakistan Private Ltd, was cited by that country's regulators for making Resochin that was lower in potency than labeled, according to inspection documents reviewed by Reuters.

A whistleblower complaint led to the discovery of more than 21 million Resochin tablets that were too weak, more than 12% under the specified weight of 400 milligrams, according to the Pakistani regulatory records.

Officials blamed the problem on a "gross failure" of manufacturing operations, citing improperly calibrated machines, poorly trained workers and insufficient staffing. Weak medications can fail to treat the illness for which they're prescribed and harm patients.

The investigation was ultimately resolved with Bayer's agreement to destroy the 21 million doses.

Regarding the 2015 incident, the company told Reuters: "All batches produced with lower content due to an error in production were never released, the corresponding batches destroyed."

According to FDA records reviewed by Reuters, the active ingredients for the drug are made at a plant in Indore, India, run by Ipca Laboratories Ltd, an Indian drug manufacturer and ingredient supplier that exports its products globally.

In 2016, the FDA issued a warning letter to Ipca regarding three of its plants in India that make chloroquine ingredients and finished pills for companies other than Bayer. The plants did not include the one making the active ingredient for Bayer's

Resochin. Nonetheless, the U.S. government sources said, Ipca's troubled history calls into question its general practices.

The FDA found the company was deleting, manipulating, and fabricating laboratory data, according to the agency's records. The company vowed at the time to "resolve these issues at the earliest."

In 2017, the agency restricted drugs and ingredients from those three plants from entering the U.S. market, a regulatory sanction called an import alert. Then in August 2019, the FDA accused one of the Ipca plants of a "cascade of failure" for not properly maintaining its quality data, agency records show.

Ipca did not respond to questions from Reuters about its track record with the FDA.

On March 20, a day after Trump praised the antimalarial drug from the podium, the FDA lifted its import alert for Ipca's chloroquine ingredients and completed tablets from the three restricted plants, according to a March 21 statement filed by Ipca with the Indian stock exchange.

The company pledged in the statement to adhere to stringent manufacturing standards, "and thus help mankind in the best possible way in these testing times."

From *Vanity Fair,* April 24, 2020

"REALLY WANT TO FLOOD NY AND NJ": INTERNAL DOCUMENTS REVEAL TEAM TRUMP'S CHLOROQUINE MASTER PLAN

By Katherine Eban

Forget testing, ventilators, and PPE. Donald Trump's big plan to beat COVID–19 involved distributing millions of doses of an unproven drug. Behind the scenes, senior administration officials pushed hard to bend the rules and back up his boasts.

On the afternoon of Saturday, April 4, **President Trump** stood at the White House podium and escalated his marketing blitz on behalf of hydroxychloroquine, hyping the old malaria drug's alleged promise in treating COVID–19, as well as his administration's success in acquiring huge amounts of it.

"We have millions and millions of doses of it—29 million to be exact," he said, as the official tally of COVID–19 cases in the U.S. topped 260,000 and governors across the country pleaded for federal support to acquire tests, ventilators, and protective gear for health care workers. "We're just hearing really positive stories, and we're continuing to collect the data." That evening, according to emails obtained by *Vanity Fair,* Trump's political appointees would ramp up the pressure on career health officials to make good on the President's extravagant promises, despite clear warnings from federal clinicians about the risks and unproven benefits of chloroquine-based treatments for COVID–19.

Vanity Fair has assembled this account based on documents and interviews provided by multiple federal officials with knowledge of internal Trump administration proceedings.

The President had been touting hydroxychloroquine for weeks, sparking worldwide shortages of the drug and prompting negotiations with Indian prime minister **Narendra Modi** to lift export restrictions on its active ingredients. But on March 24, the federal government's top interagency working group of clinicians and scientists privately threw cold water on his claims, according to a federal official with knowledge of the working group's deliberations. In an internal consensus statement, a medical countermeasures group within Health and Human Services recommended that chloroquine-based COVID–19 treatments should be studied only in controlled, hospital-based clinical trials, as their safety and efficacy was "not supported by data from reliable clinical trials or from non-human primates" and carried "potential risks." The medicines-which are used to treat malaria as well as autoimmune conditions such as lupus-can have serious side effects, including heart arrhythmias.

And yet, just hours after that April 4 press conference, White House officials pushed ahead with a massive behind-the-scenes pressure campaign on the government's top health officials to deliver huge amounts of chloroquine drugs to just about anyone who wanted them, according to documents reviewed by *Vanity Fair.* That night, **Brett Giroir,** the assistant secretary for health in the Department of Health and Human Services, sent an email with the subject line "Hydroxychloroquine" to a

group including FEMA administrator **Pete Gaynor,** HHS assistant secretary for preparedness and response **Robert Kadlec,** and Navy Rear Admiral **John Polowczyk,** who leads a supply-chain task force at FEMA.

The email read:

WH call. Really want to flood NY and NJ with treatment courses. Hospitals have it. Sick out patients don't. And can't get. So go through distribution channels as we discussed. If we have 29 million perhaps send a few million ASAP? WH wants follow up in AM. We can get a lot more of this. Right Bob? Millions per week?

The emails indicate that the administration's top health officials were closely involved in a frenzied effort to make unproven chloroquine treatments widely available, even though the FDA's new emergency rule limited distribution of the drug as a COVID–19 treatment to hospitalized patients. One hour after the first email, Gaynor replied to Kadlec, Giroir, and Polowczyk, seeming to suggest that FDA commissioner **Stephen Hahn** was on board with expanding COVID–19 patients' access to the drug: "Hahn asked to distribute to hospitals and the drug stores."

In a second email that appears to have been sent the same night, Gaynor indicated that he was working closely with Rear Admiral Polowczyk: "Me and Adm P are on it. More to follow in the am."

A FEMA spokesperson did not answer questions about the involvement of Pete Gaynor or other officials in the chloroquine plan but said, "FEMA does not maintain stocks of medicine." In response to a request for comment, an FDA spokesman responded: "Given increased demand, Dr. Hahn considered whether the donated drugs could be distributed in the commercial market to ensure a stable supply for malaria, lupus, and rheumatoid arthritis patients."

An HHS spokesperson said that, while clinical trials of the drugs proceed, some of the government's hydroxychloroquine "was provided to wholesale distributors to further supply hospitals as well as retail pharmacies that were experiencing product shortages for people who use the drug for the maintenance of chronic conditions such as rheumatoid arthritis and lupus." The spokesperson added that the hospitals and pharmacies that receive donated medications are not permitted to "charge for the drug itself."

The White House did not respond to a request for comment.

The intra-White House battle over the use of chloroquine drugs for treating COVID–19 broke into the open in dramatic fashion on April 21, when the administration's top coronavirus vaccine developer, **Rick Bright,** was pushed out of his position as the head of the Biomedical Advanced Research and Development Authority (BARDA), a small agency within HHS that partners with private scientific ventures to create vaccines, drugs, and diagnostics. The next day Bright issued a statement, first reported by *The New York Times,* stating that he was fired for resisting efforts "to fund potentially dangerous drugs promoted by those with political connections."

"Specifically, and contrary to misguided directives," he said, "I limited the broad use of chloroquine and hydroxychloroquine, promoted by the administration as a panacea, but which clearly lack scientific merit." On April 23, attorneys for Bright said they would file a formal whistleblower complaint on his behalf.

Even before Trump began making public statements from the podium, his political appointees had begun rallying around the idea of amassing chloroquine drugs to treat COVID–19, despite the paucity of evidence for their benefits. On March 18, according to records obtained by *Vanity Fair,* the German drug manufacturer Bayer first petitioned the FDA to let it donate millions of doses of a chloroquine drug called Resochin. Normally such a move would be prohibited since the FDA had never inspected the plant in Karachi, Pakistan, where Resochin is made. But the FDA set aside its usual safeguards and approved the donation, after sampling and testing the drugs to make sure they met U.S. standards. On March 19, Bayer issued a press release to announce that it was "working with appropriate agencies on an Emergency Use Authorization for the drug's use in the U.S."

The next day Trump first spoke of hydroxychloroquine from the White House podium, citing its "very, very encouraging early results. And we're going to be able to make that drug available almost immediately." Because the drug had "been around for a long time," he added, "if things don't go as planned, it's not going to

kill anybody." Trump said he had spoken the night before with New York governor **Andrew Cuomo** about the drug's promise, and "he wants to be first on line."

Inside the administration, as the White House cobbled together a plan to make chloroquine drugs widely available to the American public, Trump's political appointees began exerting tremendous and unwelcome pressure upon career health officials. As part of the plan, Oracle, the technology company co-founded by billionaire Trump fundraiser **Larry Ellison,** designed and built an app to collect data from physicians and patients tracking the response to various experimental treatments for COVID–19. (A source familiar with Oracle's app called it "an information collector; it does not recommend therapies or treatment plans.")

Under the plan, which set off alarm bells within the health agencies, chloroquine drugs would be available to patients through pharmacies, not just to hospitalized patients. "There wasn't a plan for physician oversight or monitoring," one federal official told *Vanity Fair*. "That's what concerned clinicians the most. Career FDA, NIH, CDC, and BARDA [personnel] were all very concerned about lack of physician oversight or adverse event monitoring with the expanded-access program."

On the evening of March 23, the FDA's chief counsel, **Stacy Amin,** emailed lawyers and other officials within HHS, the National Institutes of Health, and the FDA, urging action. The proposal that she relayed, as she spelled it out, was to have BARDA sponsor what is called an investigational new drug study. An IND permits a new drug in preclinical development to be shipped across state lines to be studied. In this case the IND would have covered an old drug with a potential new use. Amin, who served as a special assistant to President Trump before assuming her current role at the FDA in September 2018, wrote, "The President is announcing this tonight and I believe the WH would like it set up by tomorrow with data to flow into the Oracle platform." She then asked, "What needs to be done and what requirements do we think can be waived or use enforcement discretion?"

According to the FDA's spokesman, "The FDA, including Ms. Amin, has discussed and explored various ways to collect this data but ultimately did not support doing it through an IND, has not waived any regulatory requirements, and never sought any unapproved use of the drugs that wouldn't be under doctor supervision in connection with this or other related efforts."

The order to implement such a complex and unorthodox plan on a timetable driven by the President's press announcements stunned numerous BARDA employees. Within hours, one official wrote to a colleague, "We have been hit by a bus. Now we hit back." He said he would try to amend the proposal and find a "workable" solution.

Days of debate ensued as employees within the agency pushed back.

By late March, health officials across multiple agencies had settled on an alternate plan, which they viewed as safer for patients. On March 28, the FDA issued an emergency use authorization (EUA) to allow chloroquine drugs from the Strategic National Stockpile to be administered to hospitalized COVID–19 patients who could not access clinical trials. The stockpile is a cache of equipment and supplies managed by HHS that can be accessed in the event of medical emergencies.

In the statement related to his firing, Rick Bright seemed to refer to that authorization when he wrote, "I rightly resisted efforts to provide an unproven drug on demand to the American public. I insisted that these drugs be provided only to hospitalized patients with confirmed COVID–19 while under the supervision of a physician."

But top officials were not satisfied with the more restrictive approach and kept pushing for more widespread distribution of the drug. In an email that appears to have been addressed to Gaynor at some point after the emergency use authorization was issued, Brett Giroir argued strongly against limiting the drugs to hospitals. "NOPE. Needs to go to pharmacies as well," he wrote. "The EUA matters not. The drug is approved [and] therefore can be prescribed as per doctor's orders. That is a FINAL ANSWER."

Giroir's rationale for ignoring FDA limitations appeared to hinge on a technicality: Because chloroquine is FDA-approved for conditions including malaria and lupus, doctors could technically prescribe it for any "off-label" treatments they saw fit. He added, presumably in reference to shortages prompted by Trump's P.R. campaign, "And pharmacies need it for ON LABEL use as well."

According to Dr. **Adarsh Bhimraj,** head of the neurologic infectious diseases section of the Cleveland Clinic, the impulse to rush untested medicines to patients is understandable but unwise. "These people are sick. We want to do something," he said, drawing on his own experience treating patients with COVID–19. Nevertheless, he added, "It's important as clinicians that we step back, reflect, and pause. Let's look at the evidence before we prescribe any medications."

Dr. Bhimraj chaired the panel for the Infectious Diseases Society of America that recently issued treatment guidelines stating COVID–19 patients should only get treated with chloroquine drugs in hospital-based clinical trials. Based on the human data so far, he said, "We don't know if the benefits outweigh the harm," and only "double-blinded, placebo-controlled studies" can answer that question.

As HHS prepared to announce donations of chloroquine to the Strategic National Stockpile, and chalk up a "win" for the White House, safety concerns dogged the plan.

The FDA's chief of staff, **Keagan Lenihan,** emailed a group of federal officials including Amin to warn that after the chloroquine pills donated by Bayer arrived at John F. Kennedy International Airport in New York, they would need to be quarantined and tested. "If it is the product we think it is and it is not toxic we will release it" to the office that oversees the national stockpile, Lenihan wrote. "Apparently, where Bayer is getting this product from is a manufacturing facility they use for Africa." In fact, the facility in question is used to supply the Pakistan market, and has been inspected by Pakistani regulators, not the FDA. Lenihan continued, "Potentially serious issues with product so let's be careful when we take that win." Bayer has previously pointed out that the FDA tested Resochin "and found it to be of appropriate quality for release to the (stockpile) for emergency use."

As health officials navigated a minefield of long-standing regulations that were impeding the White House campaign, the message from the presidential podium was exultant: Trump had zeroed in on a potential cure and had slashed red tape to speed it to patients in need. On April 4, the President declared that the tech giant Oracle had donated a "very sophisticated" web portal to gather real-time data on how patients were responding to the new treatments.

Since then, a steady drumbeat of small-scale studies and medical recommendations has cast increasing doubt on the treatment that Trump once hailed as a "game-changer." On April 21, a study of 368 COVID–19 patients at veterans hospitals showed that about 28% of those treated with hydroxychloroquine died, compared with 11% of those who didn't receive the medication.

On the same day the National Institutes of Health issued detailed treatment guidelines, stating, "There are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID–19." The agency advised clinicians using the drugs to closely monitor patients for adverse effects, particularly cardiac risks.

Whether owing to the accumulation of evidence against hydroxycholoroquine's efficacy, the resistance of career health officials, or something else entirely, the Trump administration appears to have dropped its crusade on behalf of the purported miracle cure-at least for now. It's been over a week since the president last used a daily coronavirus briefing to promote the drug. This week, the U.S. death count from COVID–19 is expected to pass 50,000.

From *Vanity Fair,* May 5, 2020

"Political Connections and Cronyism": In Blistering Whistleblower Complaint, Rick Bright Blasts Team Trump's Pandemic Response

By Katherine Eban

> Two weeks after being pushed out of his post, the former head of a $1.5-billion federal health agency formally accuses top officials of pressuring him to approve unproven chloroquine drugs and award pricey contracts to friends of the administration.

He was pressured to invest in drugs and vaccines that lacked scientific merit, because the people selling them had friends in the Trump administration, up to and including the President's son-in-law, **Jared Kushner.** He was forced to transfer funds to acquire drugs for the Strategic National Stockpile, America's most impor-

tant reserve of lifesaving medications, based not on health needs but on "political connections and cronyism." He was instructed to use his department's budget to purchase flu medications of questionable efficacy. And when the COVID–19 crisis erupted, he was pressured to approve a plan that would "flood" cities with unproven and untested doses of chloroquine drugs, from uninspected manufacturing plants in Asia. When his efforts to work through the system failed, he decided he had a "moral obligation to the American public" to ring the alarm about the plan, "which he believed constituted a substantial and specific danger to public health and safety." In retaliation, he was "smeared," with officials unfairly accusing him of dropping the ball on vaccine development and PPE preparation.

These are just some of the allegations contained in a blistering, 63-page complaint that Dr. **Rick Bright,** former head of the Biomedical Advanced Research and Development Authority (BARDA), filed today with the U.S. Office of Special Counsel. According to his lawyers, Bright will testify before Congress next week.

Vanity Fair has submitted requests for comment to the White House and the Food and Drug Administration, and will update this article with any responses. In a statement, Department of Health and Human Services spokesperson Caitlin Oakley said: "Dr. Bright was transferred to NIH to work on diagnostics testing—critical to combatting COVID–19—where he has been entrusted to spend upwards of $1 billion to advance that effort. We are deeply disappointed that he has not shown up to work on behalf of the American people and lead on this critical endeavor."

Bright has become the first high-level federal whistleblower to publicly allege that the Trump administration has responded to the COVID–19 crisis by unduly pressuring health officials, and putting politics and profit ahead of science. Bright, the government's top coronavirus vaccine developer, had spent a decade at BARDA, a small but powerful agency within the Department of Health and Human Services (HHS), whose mandate is to partner with private companies to help accelerate the development of vaccines, drugs, and diagnostics. According to Bright's complaint, BARDA manages almost $50 billion worth of contracts and acquisitions, on an annual budget of just over $1.5 billion. He was named director in 2016.

On April 22, after HHS reassigned him to a smaller role at the National Institutes of Health, Bright alleged in a fiery statement that he had been sidelined because he "resisted efforts to fund potentially dangerous drugs promoted by those with political connections." One of the drugs Bright identified in his statement was the malaria medication hydroxychloroquine, which **President Trump** had promoted extensively as a "game changer." Bright said he had "rightly resisted efforts to provide an unproven drug on demand to the American public."

His original statement prompted an immediate call for investigations. Rep. **Frank Pallone Jr.** (D–N.J.), chairman of the House Energy and Commerce Committee, asked the HHS inspector general to probe Bright's departure, and Rep. **Anna G. Eshoo** (D–CA.) announced that her subcommittee on health would hold congressional hearings.

Today's complaint goes much further, enumerating a series of instances in which politics encroached on science. According to the complaint, Bright's superiors at the Department of Health and Human Services began pressuring him to "ignore expert recommendations and instead to award lucrative contracts based on political connections and cronyism," starting around the spring of 2017. Bright says he "repeatedly clashed" with his boss, Dr. **Robert Kadlec,** the assistant secretary for preparedness and response, over the "outsized role" played by Kadlec's friend **John Clerici,** a pharmaceutical consultant. That year Clerici tried to get Bright to renew a contract with one of his clients, Aeolus Pharmaceuticals, that was set to expire. "In attempting to justify the extension of this failed contract," Bright says in his complaint, "Mr. Clerici emphasized that Aeolus's Chief Executive Officer was a 'wildcard' and a friend of Jared Kushner, President Trump's son-in-law and a Senior Advisor to the President."

In a statement to *The New York Times,* Clerici said, "I unequivocally deny all of the allegations lodged by Dr. Bright and his lawyers."

Tensions escalated over the course of the next year, the complaint alleges, as Bright objected repeatedly to Kadlec's efforts to award multimillion-dollar contracts to Clerici clients. Last fall Bright "rejected pressure by Dr. Kadlec to invest millions of dollars in EIDD–2801, a drug developed at Emory University by a longtime friend of Dr. Kadlec. EIDD–2081 was presented as a 'miracle cure' for influenza, Ebola, and nearly every other virus, even though the developer had not yet conducted clinical trials and no data had been compiled to demonstrate either the efficacy or safe-

ty of the drug in humans." That incident, the complaint says, further strained Bright's relationship with Kadlec, setting the scene for their eventual rupture over COVID–19. "The fact that Dr. Kadlec and his staff repeatedly made decisions to benefit those like Mr. Clerici and his clients, but which were not in the best interest of the health or safety of Americans, continued to be of tremendous concern to Dr. Bright," the complaint states.

The COVID–19 crisis only magnified the brewing conflict between scientific safeguards and political expediency. In a January 23 meeting, Bright demanded urgent access to funding, personnel, and clinical specimens necessary to develop lifesaving medicines for use in a possible pandemic. He was met with reassurances from HHS brass that the virus's spread was under control, according to the complaint. Also in January, **Mike Bowen,** the co-owner of a leading mask manufacturer named Prestige Ameritech, offered to scale up production of N95 masks. "U.S. mask supply is at imminent risk," Bowen told Bright, according to the complaint. Bowen reached out again and again in the coming days, but Bright was unable to get Kadlec and HHS to take the threat seriously, the complaint states, leading Bowen to write to Bright, saying, "Rick, I think we're in deep shit."

Bright's allegations, and his refusal to accept his demotion quietly, come as the Trump administration continues to muzzle scientists and remove government watchdogs. On Friday, House Democrats said that the White House had blocked the government's top infectious disease expert, Dr. **Anthony Fauci,** from testifying at an upcoming appropriations panel hearing. That same day Trump nominated a new Health and Human Services inspector general, effectively replacing the acting official who had issued a report in early April confirming that hospitals around the country were experiencing widespread shortages of critical medical supplies and protective equipment. The administration had denied that such shortages existed.

The crisis at BARDA came to a boiling point after top agency health officials found themselves under immense pressure to fulfill a vision that Trump had outlined from the White House podium: to build a stockpile of repurposed malaria drugs, hydroxychloroquine and chloroquine, that he claimed had "very, very encouraging early results."

There was scant evidence of the drug's utility—and plenty of questions about its safety as a treatment for COVID–19. Chloroquine drugs, which are used to treat malaria as well as autoimmune conditions such as lupus, can have serious side effects, including heart arrhythmias. One infectious disease doctor described hydroxychloroquine as a "zombie drug," advanced as a possible treatment for acute respiratory distress in various outbreaks, including the H5N1 and H7N9 strains of avian flu, with disappointing results. "It's back every seven years."

It is unclear what, exactly, drew Trump administration officials to double down on hydroxychloroquine as a potential game-changing cure. On March 13, a Google Doc on the use of chloroquine drugs, which had been cobbled together by a cryptocurrency investor and a New York City lawyer, drew the attention of billionaire inventor Elon Musk, who tweeted about it on March 16.

By March 17, according to documents obtained by *Vanity Fair,* officials within HHS were already working to corral donations of the drug, though they seemed to know it was unlikely to amount to a miracle cure. "Not a blockbuster drug for this fight, but a good drug" is how **Joe Hamel,** the manager of strategic innovation and emerging technology at the Assistant Secretary of Preparedness and Response (ASPR), a division within HHS, described chloroquine treatments in an email to colleagues.

The next day a health scientist at BARDA noted to colleagues that the guidance from two HHS working groups was to "wait for clinical data on the numerous clinical trials that are ongoing before making recommendations on the use of chloroquine for COVID–19. Currently, there is no data available to support that chloroquine provides clinical benefit in the treatment or prevention of COVID–19."

But Trump did not wait. On March 19, he first touted the drug at a White House press conference, setting off a crisis that ricocheted from the Food and Drug Administration (FDA) to HHS to BARDA, as staff looked to circumvent safeguards and load up the Strategic National Stockpile with millions of doses, procured from far-flung manufacturing plants around the globe. (The Strategic National Stockpile is a cache of equipment and supplies managed by HHS that can be accessed in the event of medical emergencies.)

This left Dr. Bright, and other top administration health officials, scrambling for answers to urgent questions about the quality, safety, and efficacy of the drugs. The debate played out inside contentious White House coronavirus task force meetings and a flurry of emails, as documents obtained by *Vanity Fair* reveal.

According to Dr. **H. Clifford Lane,** deputy director for clinical research and special projects at the NIH's National Institute of Allergy and Infectious Diseases (NIAID), the administration proposed that the NIH launch a massive study involving as many as tens of thousands of patients. It was an idea that the NIAID flatly rejected. "We were very keen to do some studies, to figure out what effect the drug does have," Lane says, "but in the traditional way we do it"—meaning via smaller-scale studies on hospitalized patients who could be closely monitored and evaluated.

Nonetheless, on or around March 23, administration officials devised a plan for Bright's agency, BARDA, to sponsor a new experimental drug study, under which the chloroquine drugs could be widely disseminated.

The scheme set off a furious round of debate within HHS, as BARDA officials pushed back, concerned that broad use of the drug could pose a clinical danger to the American public.

By late March, health officials across multiple agencies had settled on an alternate plan, which they viewed as safer for patients. On March 28, the FDA issued an emergency use authorization (EUA) to allow chloroquine drugs from the Strategic National Stockpile to be administered to hospitalized COVID–19 patients who could not access clinical trials. As Bright said in a statement on his firing, "I insisted that these drugs be provided only to hospitalized patients with confirmed COVID–19 while under the supervision of a physician."

But top officials appear to have ignored the restriction that Bright fought to insert into the FDA's emergency rule. As Trump continued to expound on the benefits of hydroxychloroquine from the podium, they worked behind the scenes to move thousands of doses from the stockpile into the nation's retail pharmacies, where patients could access the drug with a simple doctor's prescription. In part, this was intended to assist non-COVID–19 patients struggling with shortages prompted by the president's promotion of the drug, but there was also discussion of "off-label" prescriptions for treatment of the novel coronavirus.

On April 5, Navy Rear Admiral **John Polowczyk,** who leads a supply-chain task force at FEMA, spelled out the distribution plan in an email to top administration colleagues: "Distro to Hospitals and retail pharmacies and geography: NYC area—100k to hospitals, 150k to retail Detroit—50k to hospitals, 100k to retail Chicago—50k to hospitals, NO—20k hospitals—50k retail Total hospitals—220k hospitals, 400k retail. Total 620k first shipments."

This resulted in a query from an official within ASPR's Strategic National Stockpile division: "All, just wanted to assure everyone is aware that the EUA," the FDA's emergency rule, "for hydroxychloroquine and chloroquine appears to limit use to the treatment of hospitalized patients." A FEMA spokesperson referred questions about the distribution plan described by Polowczyk to HHS and the FDA.

But with Trump cheerleading wide use of the drug, his top appointees appeared uninterested in the more restrictive fine print. Only after a study of veterans with COVID–19 found that patients treated with chloroquine died at twice the rate of those who didn't get the drug did Trump scale back his cheerleading. By then Rick Bright had fought all he could within the system to limit the drug's use. Within a week of the study's publication, Bright had been pushed out of BARDA and decided to blow the whistle.

From *Vanity Fair,* May 14, 2020

"HE WAS FIRED FOR BEING RIGHT": RICK BRIGHT WARNS CONGRESS "TIME IS RUNNING OUT" TO CONTAIN CORONAVIRUS

By Katherine Eban

As Trump rage-tweeted and representatives bickered amid bottles of hand sanitizer, the ousted head of BARDA described trying to mount an effective federal response to COVID–19—and paying a heavy price.

The United States could be facing "the darkest winter in modern history," according to testimony this morning by Dr. **Rick A. Bright,** the federal government's top vaccine developer turned whistleblower. Speaking in steady, measured tones at a widely anticipated hearing before the House Energy and Commerce Committee's Subcommittee on Health, Bright warned that, without a "standard, centralized, coordinated plan to take our nation through this response" to the COVID–19 crisis, the federal government risked a resurgence of the virus that could "be devastating."

"The window is closing to address this pandemic," Bright testified. "Time is running out because the virus is still spreading everywhere."

The hearing marked the first time that a top government scientist has testified candidly, and in unstinting detail, about the shortcomings of a federal response that, as Bright described it, has been dominated by politics, cronyism, and falsehoods, rather than science.

Members of Congress, wearing latex gloves and masks and seated amid containers of Clorox wipes and hand sanitizers, sparred over the claims made by Dr. Bright, who remained calm throughout the more-than-three-hour hearing. Wearing a gray suit and crisp red tie, he testified that the administration needed to "be truthful with the American people" about the "real risk and dire consequence of this virus."

Asked by Rep. **Anna Eshoo** (D–CA), the committee chairwoman, to say whether the Trump administration's response to the pandemic had been a success or a failure, Bright paused, then said, "I believe we could have done better. . . . There are critical steps we did not take in time." However, there was no mistaking his view of the administration's failures. As he testified later in the hearing, "We don't have a single point of leadership right now . . . and we don't have a master plan for this response."

His stark testimony came in a week when Dr. **Anthony Fauci,** alongside other top health officials, testified before a Senate panel and warned that reopening the economy too soon could lead to a resurgence "that you may not be able to control."

On Tuesday the U.S. Office of Special Counsel stated in a letter to Bright's lawyers that it had found a "substantial likelihood of wrongdoing" by the Department of Health and Human Services in removing Bright as head of the Biomedical Advanced Research and Development Authority, a small but powerful agency within HHS, whose mandate is to partner with private companies to help accelerate the development of vaccines, drugs, and diagnostics. BARDA manages almost $50 billion worth of contracts and acquisitions, on an annual budget of just over $1.5 billion. Bright was named director in 2016.

The OSC has given the HHS secretary, **Alex Azar,** 60 days to conduct an investigation into Bright's removal and report his findings. On April 22, after HHS reassigned him to a smaller role at the National Institutes of Health, Bright alleged in a fiery statement that he had been sidelined because he "resisted efforts to fund potentially dangerous drugs promoted by those with political connections." Chief among those drugs was the malaria medication hydroxychloroquine, which **President Trump** had promoted extensively as a "game changer."

On May 5, Rick Bright filed a 63-page whistleblower complaint with the OSC. That unleashed a furious public relations battle within Health and Human Services to contain the fallout from his allegations, and to paint Bright as a mediocre leader of BARDA who served as an obstacle to innovation, rather than as a steward of it.

In a three-page statement issued this morning, HHS said it "strongly disagrees" with Dr. Bright's allegations, and accused him of working with "partisan attorneys who are politicizing the response to COVID–19. His whistleblower complaint is filled with one-sided arguments and misinformation." The statement also accused him of continuing to draw a government salary and failing to take up the new position offered to him. "Rick Bright has chosen to stay home," the statement said.

In a statement, Dr. Bright's lawyers countered HHS' claims, saying that Dr. Bright "never refused" to report to his new post at the National Institutes of Health and planned to do so next week, unless HHS secretary Alex Azar "grants a stay of his reassignment," as requested by the Office of Special Counsel. They also added, "Rather than investigating Dr. Bright's serious allegations of wrongdoing . . . HHS leadership has decided to lodge baseless allegations against him in an effort to distract attention" from essential issues that should be addressed to save lives.

This morning, in anticipation of today's hearing, President Trump tweeted, "I don't know the so-called Whistleblower Rick Bright, never met him or even heard of him,

but to me he is a disgruntled employee, not liked or respected by people I spoke to and who, with his attitude, should no longer be working for our government!"

In her opening statement, Rep. Eshoo said that Bright had filed "one of the most specific and troubling whistleblower complaints I have ever seen," and stated, "He was fired for being right."

Rep. **Michael Burgess** (R–TX) accused Rep. Eshoo of trampling on minority rights and of "procedural fouls" in setting up the hearing.

Over the course of three hours, Bright testified that his urgent warnings to top Health and Human Services officials from January through March about a critical shortage of needed supplies—from syringes and swabs to personal protective equipment for health care workers—led to his being cut out of key, high-level meetings. "I was told that my urgings were causing a commotion, and I was removed from those meetings," he said.

But he said it was his opposition to a Trump administration plan to promote broad access to an unproven and potentially dangerous drug, chloroquine, for use in treating COVID–19, that led to his removal from his post at BARDA.

The battle over hydroxychloroquine within the administration began in mid-March, as President Trump hailed the malaria drug as a "game changer" for COVID–19, a claim that sparked worldwide shortages of the drug and a frantic effort inside the administration to build a stockpile of the medicine and find a way to disseminate it widely.

Regulations and long-relied-upon safeguards stood in the way, as career health officials at HHS and the FDA faced tremendous pressure to help implement the Trump administration's plan. Top officials clashed over a push for the FDA to approve a donation from Bayer of 3 million pills of a chloroquine drug, Resochin, which had been made in manufacturing plants in India and Pakistan that had never been inspected by the FDA.

At BARDA, Bright was asked to sponsor an investigational new drug study, as a legal and organizational mechanism to disseminate the drugs. Bright pushed back, saying that he opposed a plan that would allow Americans wide access to the drugs without close supervision from their doctors.

As he testified at today's hearing, it was a lack of limited clinical data as well as concerns about the drug's known cardiac risks that made him push for "carefully controlled clinical studies under the close watchful eye of a physician."

Bright went on to say that he was removed, in part, in retaliation for pushing back against making chloroquine drugs more widely available to Americans, even those who might not actually be infected, outside of more closely supervised hospital settings.

Bright testified that he had been briefly reassured when the FDA passed an emergency rule that required chloroquine drugs in the stockpile to be used only for hospitalized patients. But he said his "concerns were escalated" once he learned that HHS leadership continued to push to make the drugs available outside of that rule.

Expressing those concerns, he testified, was "the straw that broke the camel's back."

Asked by Rep. **John Sarbanes** (D–MD) about what needed to be done to improve the government's response, Bright said, "We need to unleash the voices of the scientists in our public health systems in the United States so they can be heard."

From *Vanity Fair*, May 27, 2020

"I'LL SEND YOU THE CONTACT": DOCUMENTS EXPOSE FDA COMMISSIONER'S PERSONAL INTERVENTIONS ON BEHALF OF TRUMP'S FAVORITE CHLOROQUINE DOCTOR

BY KATHERINE EBAN

> Looking past concerns about the drug's safety, not to mention his own agency's recommendations, Stephen Hahn took time during the COVID–19 crisis to lend a helping hand to Dr. Vladimir Zelenko, a hero among fringe Trumpworld figures.

It was Sunday, April 5, and Dr. **Stephen Hahn,** the commissioner of the U.S. Food and Drug Administration, faced a world of problems. Less than two months after

the first American death from COVID–19, the U.S. health care system was under siege, with more than 300,000 confirmed cases of the new disease-the most of any nation in the world-and almost 10,000 deaths. Hahn was under fire over faulty test kits the FDA had approved, and angry members of Congress were demanding that his agency prevent the hoarding of an old malaria drug called hydroxychloroquine, which **President Trump** was hyping without evidence as a miracle cure.

Nevertheless, Dr. Hahn found time that afternoon to carry out an unusual mission. He contacted an obscure family practitioner in Monroe, New York, with whom he had never before been in touch, to ask if the doctor had "time for a quick call." Once on the phone with Dr. **Vladimir Zelenko,** Hahn posed a question: How could he—the commissioner of a federal health agency with a $5.7-billion annual budget and the responsibility to safeguard the nation's drugs, medical devices, and food supply—be of help?

Zelenko was a 46-year-old "simple country doctor," as he described himself to *The New York Times,* who claimed to have witnessed positive results after prescribing a cocktail of drugs including hydroxychloroquine to patients in the Orthodox Jewish community of Kiryas Joel, New York. His message aligned perfectly with the pronouncements Trump had been making from the White House podium: that hydroxychloroquine, when used early and liberally, was a game-changing treatment for COVID–19. That, in turn, had earned Zelenko a growing platform on right-wing media.

Two days after that first phone call, in a series of text messages obtained by *Vanity Fair,* Zelenko returned to Hahn for help setting up a clinical trial of some 750 outpatients at St. Francis Hospital in Roslyn, New York. "The Catholic Health System (St. Francis Hospital)/Dr. Zelenko COVID–19 trial is ready to go," Zelenko wrote to Hahn, copying one of the hospital's doctors involved in the trial. "We need ASAP 1. Hydroxychloroquine 200mg. 10,000 pills 2. Azithromycin 500mg 5,000 pills 3. Zinc sulfate 220 mg 5,000 pills. This treatment will be deployed in outpatient primary care."

Hahn responded, "Not sure what the ask of FDA is." To which Zelenko replied, "We need the medication to run the study." Hahn then asked, "Do you have IRB approval?" This referred to an institutional review board that hospitals use to oversee clinical trials and research. The doctor answered, "Hopefully this week."

"Congratulations," Hahn offered. "Really well done." He then advised the doctor to reach out to the Federal Emergency Management Agency (FEMA) to obtain hydroxychloroquine from the Strategic National Stockpile, a federal cache of emergency equipment and supplies managed by the Department of Health and Human Services (HHS). When the doctor expressed uncertainty over how to do that, Hahn offered, "I'll send you the contact."

Federal agency chiefs normally focus on high-level problems and solutions, delegating any ground-level efforts through the chain of command. Assisting with a lone clinical trial hardly seemed worthy of the commissioner's time. More troubling, perhaps, was the question of why Hahn-whose agency two weeks earlier had established restrictions on the use of certain chloroquine drugs in the national stockpile to hospitalized patients, as a way to avert potential risk to patients-appeared to be bending over backward to assist a doctor who, in line with President Trump, was advocating unfettered use of the drug.

Hahn, 60, a radiation oncologist who previously served as chief medical executive of the University of Texas MD Anderson Cancer Center, has repeatedly insisted that he has felt no political pressure while carrying out his agency's pandemic response. "I can assure you 100% that the President has never pressured me to make a decision regarding any regulatory aspect of the FDA's work," he recently told *The Washington Post.*

But Hahn's previously unreported intervention on behalf of Zelenko—who was both promoting a COVID–19 treatment that the government's top medical experts had warned against and seeking drugs that the FDA's own rules restricted—calls his claims of independence into doubt. "I am pretty appreciative to Stephen Hahn," Zelenko told *Vanity Fair* in an interview. "I think he helped in this process."

The FDA declined *Vanity Fair*'s request to interview Dr. Hahn. FDA spokesman **Michael Felberbaum** instead provided a statement: "Throughout the pandemic, the FDA has heard from people across all levels of government, academia, industry, and the public interested in providing or seeking assistance or information from the agency. In that vein, Dr. Hahn and others at the FDA have connected with a variety

of entities on ways to combat COVID–19 and put them in touch with the appropriate people for follow-up, including agency staff who assess the science and the data regarding potential prevention and treatment options."

But experienced observers of the FDA find Hahn's conduct troubling. "The primary import of his action is to add the agency's scientific weight to these unproven claims put forth by Trump and Zelenko," said Dr. **Peter Lurie,** president of the Center for Science in the Public Interest and a former associate FDA commissioner. "It feels like so much about Trump and this epidemic. You say one thing and you encourage something else. 'We're providing it under restricted conditions, but—*wink-wink*—you have little to fear in providing it in situations beyond that.'"

In the weeks following their first phone call, as Hahn continued to assist Zelenko, the commissioner found himself a party to Zelenko's growing political entanglements. By April 26, Hahn had been copied on an email alongside Trump chief of staff **Mark Meadows** and former New York City mayor turned Trump lawyer **Rudy Giuliani.** The email was sent to Zelenko by **Jerome Corsi,** a right-wing conspiracy theorist who had been investigated as part of the Mueller probe. In it, Corsi—who is involved in a for-profit telemedicine platform where doctors prescribe hydroxychloroquine—expressed his anxieties about the "heavy legal scrutiny" facing the drug.

A growing body of clinical studies indicates that hydroxychloroquine is ineffective in treating COVID–19 and may actually increase mortality. The World Health Organization, the National Institutes of Health, the FDA, and the pharmaceutical company Sanofi, which sells hydroxychloroquine under the brand name Plaquenil, have all issued guidelines cautioning against the kind of early, prophylactic use of the drug that Trump has hyped and Zelenko advocates. On Friday a retrospective study of 96,000 COVID–19 patients on six continents, published in the medical journal *The Lancet,* found that hospitalized patients treated with hydroxychloroquine and an antibiotic—part of the drug combination Zelenko has plugged—were 45% likelier to die.

Zelenko claims that clinical trials of hydroxychloroquine with poor outcomes are part of a political conspiracy from a "corrupted" medical establishment, and are "clearly designed to fail and to substantiate a false narrative." Last week Trump claimed, honestly or not, that he himself had been taking hydroxychloroquine.

President Trump began touting hydroxychloroquine from the White House podium on March 19, claiming there were "very, very encouraging early results." Dr. Hahn, who was also present, offered a more measured assessment, stating that "a large, pragmatic clinical trial" could help answer the question of the drug's effectiveness.

His caution reflected the doubts of top federal clinicians and scientists. In early March, the director of the influenza and emerging infectious diseases division within HHS's Biomedical Advanced Research and Development Authority (BARDA) wrote to a colleague that the drug had "not panned out to clinical benefit," according to an internal email obtained by Vanity Fair. Others flagged the drug's well-established risk of cardiac arrhythmias.

Nonetheless, the White House was moving ahead with a plan to promote the drug and launch a vast clinical trial. On March 19, Trump alluded to that plan when he declared that the government would be "quickly studying this drug . . . as it's given out to large groups of people, perhaps in New York and other places."

Two days after that press conference, Dr. Zelenko uploaded a video to YouTube in which he addressed the president directly. Zelenko claimed that he had used hydroxychloroquine early on hundreds of patients, not a single one of whom had been hospitalized. He even advocated treating patients with his regimen of hydroxychloroquine, zinc, and azithromycin *before* confirming a diagnosis, as he believed clinical intuition was more important than a positive test. In the video, he told Trump, "I am suggesting that you please advise the country that they should be taking this medication in an outpatient setting." He added, "I personally love you."

The day after Zelenko uploaded the video, Trump's chief of staff, Mark Meadows, contacted him to ask for his patient data. Meadows did not respond to an email seeking comment.

Two days later, on March 24, the federal government's top interagency medical countermeasures group recommended that chloroquine-based COVID–19 treatments should be studied only in controlled, hospital-based clinical trials, as their safety and efficacy were "not supported by data from reliable clinical trials" and carried "potential risks." On March 28, the FDA issued its EUA allowing chloroquine drugs

from the Strategic National Stockpile to be administered only to hospitalized COVID–19 patients who could not access clinical trials.

Remarkably, the recommendation did nothing to curb the Trump administration's ambition to "flood New York and New Jersey" with treatment courses obtainable even at drugstores, as spelled out in a series of internal emails first obtained by *Vanity Fair.* Inside the federal government, career officials had been pushing back for weeks against a White House plan they considered dangerous, but by the evening of Saturday, April 4, it was clear that Hahn had fallen in line with the administration. "Hahn asked to distribute to hospitals and the drug stores," FEMA administrator **Peter Gaynor** wrote to colleagues in an internal email.

It was the following day when Hahn first reached out to Zelenko.

Hahn's services on behalf of Zelenko included a personal introduction to the director of the National Library of Medicine, a division of the National Institutes of Health that oversees *clinicaltrials.gov,* the website where any legitimate clinical trial must be listed in order to publish study results in a peer-reviewed journal. In a statement, a spokesperson for the National Library of Medicine said that Zelenko had contacted the director, **Patricia Flatley Brennan,** and "shared lessons learned from treating patients that he thought would be valuable to others. Dr. Brennan suggested that he write up a case report for publication."

As Zelenko worked with St. Francis Hospital to hammer out the details of a clinical trial that would test his preferred cocktail of hydroxychloroquine, zinc, and one of two antibiotics—azithromycin or doxycycline—on COVID–19 outpatients, Hahn intervened. He shared the contact information for a FEMA official with hospital investigators, so St. Francis could obtain hydroxychloroquine directly from the Strategic National Stockpile.

"Stephen Hahn helped us get medication," Zelenko said. "We were having trouble-he advised us who to talk to in FEMA."

One current HHS official said of Hahn's intervention to help a single hospital get stockpiled drugs, "That is way outside what one would consider normal for a commissioner to do. . . . I have never heard of anyone at FDA doing anything like that."

Dr. **Avni Thakore,** a cardiologist at St. Francis Hospital and the study's principal investigator, told *Vanity Fair* that the study of hydroxychloroquine in COVID–19 patients seemed like a natural fit for the hospital, which has a national reputation in cardiac care. "It is a safety protocol," she said of the study, which plans to remotely monitor the heart rhythms of trial enrollees by providing them with mobile electrocardiogram devices. She also emphasized that the trial was inspired not only by Zelenko's clinical observations, but also by other sources: "early results from some small studies, and observational reports, doctors sharing their observations, all of that combined."

As Zelenko's celebrity grew, he became a fixture on podcasts hosted by Jerome Corsi and, through him, Rudy Giuliani. Before long, Corsi himself would contact Hahn.

Corsi, who obtained a Ph.D. in political science from Harvard in 1972, is the best-selling author of books questioning **John Kerry's** war record and **Barack Obama's** citizenship. He briefly served as the Washington, D.C., bureau chief of Infowars, the conspiracy website run by Sandy Hook truther **Alex Jones,** though he later sued Jones for defamation. He became a target of the Mueller investigation as a result of his contacts with **Roger Stone** and his alleged foreknowledge of WikiLeaks document dumps. The Mueller team eventually declined to press charges, and Corsi sued Stone for defamation.

In late April, Corsi was planning a promotional campaign for a telemedicine platform on his website, *corsination.com,* that enabled doctors to conduct video consultations with patients and directly prescribe them hydroxychloroquine and other drugs. According to Corsi's marketing materials, Dr. Zelenko would serve as the program's medical director.

But on April 20, Corsi accidentally emailed those marketing plans not to Zelenko but to **Aaron Zelinsky,** a U.S. prosecutor who'd worked on the Mueller investigation—a mishap first reported by *The Washington Post.* Zelinsky, now spearheading a COVID–19 fraud-fighting task force out of the Maryland U.S. Attorney's Office, scrutinized the materials and zeroed in on Corsi's claim that "Zelenko has an FDA approved randomized test of HCQ under-way." No such trial was listed on *clinicaltrials.gov,* raising the prospect of fraud.

Zelenko said he had mistakenly made the claim to a group of physicians in the telemedicine program, having confused approval from the hospital's institutional review board with FDA approval. "I kind of misspoke," he told *Vanity Fair*. He also said he had agreed to serve as an unpaid medical adviser, not a paid director, for Corsi's telemedicine program.

When Zelinsky inquired about the erroneous claim, Corsi and Zelenko panicked. Zelenko appealed for help to a doctor at St. Francis Hospital who was one of the study's principal investigators. The doctor wrote a "To Whom It May Concern" letter on April 22, stating: "Dr. Zelenko not only embraced the idea of a controlled trial, but has been instrumental in helping us develop the trial to the point where, in less than two weeks, we are ready to initiate it."

On Sunday, April 26, Corsi expressed his concerns in an email to Zelenko that *Vanity Fair* obtained. Corsi cc'd the message to a large and unlikely group: Dr. Hahn; Mark Meadows (via his personal email); Giuliani; a volunteer paramedic director in Orange County; a rabbi; the lawyers for Corsi and Zelenko; and two of the doctors involved in the fledgling St. Francis clinical trial. (Reached by *Vanity Fair*, Corsi declined to comment on his decision to copy Hahn and the others on the email.)

Corsi noted in the email that the "HCQ issue is under heavy legal scrutiny." Taking Zelenko to task for making inflated scientific claims about his protocol, Corsi wrote, "I am concerned that you have to speak very precisely." He went on to stress how scrupulous he had been about following the letter of the law in setting up the TeleMD program: "under advice by legal counsel, emphasizing that we are marketing a teleconference with an MD who can legally write prescriptions for HCQ."

The email had the quality of skywriting, as if it were intended to telegraph to the email recipients, and to any federal prosecutor, Corsi's commitment to scientific legitimacy. It is not clear what impact the email had. But one recipient of the email described it as a "CYA" effort.

The doctors at St. Francis Hospital, who were copied on the email, submitted their clinical trial design to *clinicaltrials.gov* that same day, though it is unclear whether they did so before or after receiving Corsi's email. Within six days the trial was posted on the website, complete with what appeared to be an imprimatur of legitimacy, a National Clinical Trial number.

In an interview, Corsi was keen to assert his view that the posting of the clinical trial "makes legitimate what Dr. Zelenko was saying . . . on a government website, a government-recognized clinical trial."

From *The New England Journal of Medicine,* June 11, 2020

DRUG EVALUATION DURING THE COVID–19 PANDEMIC

By Benjamin N. Rome, M.D., and Jerry Avorn, M.D.

The search for a treatment for COVID–19 is testing our country's ability to quickly develop, test, and deploy medications, presenting both opportunities and challenges to our drug-assessment apparatus. Several aspects of the U.S. response raise serious concerns, highlighting how the processes for evaluating and approving drugs can go awry during a public health crisis.

The global pandemic has put pressure on clinicians and the Food and Drug Administration (FDA) to act swiftly to make medications available to patients. When very limited observational and anecdotal evidence raised the possibility that the antimalarial drugs chloroquine and hydroxychloroquine may have activity against SARS–CoV–2, President Donald Trump quickly began celebrating the promise of their widespread use, stating on national television that he had a "hunch" that such therapy was effective and that the drugs could be a "game changer" in addressing the pandemic. More recently, he openly encouraged patients to take the drugs and suggested he might do so himself, despite having tested negative for the virus.

After Trump's initial assertions, the FDA—still facing criticism that its delays in approving testing kits for the virus hindered prevention efforts—issued an Emergency Use Authorization (EUA) on March 28 that allowed for use of the drugs to treat patients with COVID–19. Although the EUA's scope was limited to permitting distribution of chloroquine and hydroxychloroquine from a federal stockpile, its issuance was widely yet incorrectly reported by Trump and others as meaning that the FDA had approved the drugs for this indication. The Centers for Disease Con-

trol and Prevention (CDC) went so far as to publish doses of chloroquine and hydroxychloroquine for use in patients with COVID–19, though it later removed them from its website. Meanwhile, serious concerns have been raised about the adequacy of the available studies of these drugs.[1]

These developments represent fundamental threats to the U.S. drug-evaluation process. Advocating that the FDA should quickly approve drugs without randomized trial data runs counter to the idea of evidence-based medicine and risks further undermining the public's understanding of and faith in the drug-review process, which requires "substantial evidence" of safety and efficacy based on adequate and well-controlled trials before a drug can be marketed. Though this unprecedented emergency provides a compelling reason for the FDA to act as efficiently as possible, the agency and the medical community can still maintain the highest scientific standards while acting expeditiously.

The new EUA represents only the second time the FDA has ever used emergency authority to permit use of a medication for an unapproved indication. During the 2009–2010 "swine flu" outbreak, the agency allowed use of peramivir—an investigational intravenous neuraminidase inhibitor—in severely ill hospitalized patients with H1N1 influenza. Under that EUA, peramivir was administered to some 1,200 to 1,500 patients, with no rigorous tracking of which patients received it or collection of outcome data.[2] Ultimately, a randomized, controlled trial failed to show any benefit of peramivir as compared with placebo in severely ill hospitalized patients with influenza; the drug was approved in 2014 with an indication only for uncomplicated influenza and not for use in severely ill hospitalized patients.

Hydroxychloroquine is already marketed for other conditions, so physicians were allowed to prescribe it off-label to patients with COVID–19 even before the EUA or CDC dose recommendations were issued. In addition, for investigational drugs that are not yet marketed, providers can request "expanded access" for severely ill patients who lack alternative treatment options and are not eligible for clinical trials—permission the FDA nearly always grants. This option has already been used for remdesivir, an investigational antiviral drug whose manufacturer has provided it to more than a thousand patients with COVID–19 outside clinical trials.

Even before the pandemic, many conservative and libertarian politicians and advocacy groups supported expanding patients' "right to try" unapproved experimental drugs. This position has intensified a commonly held but spurious belief that slow processes and overly onerous requirements by the FDA prevent patients from accessing many clinically useful drugs. In fact, the FDA presides over one of the fastest drug approval processes in the world, with a majority of drugs gaining approval in the United States before they are approved in Europe or Canada.[3] The FDA approves the overwhelming majority of drug applications it receives, and over the past several decades it has been approving more drugs on the basis of limited evidence, such as fewer clinical trials per drug, trials with suboptimal design, and trials using surrogate measures—which may or may not predict actual clinical benefit—as end points.[4]

Widening access to experimental therapies that have not been fully evaluated is likely to have several unintended consequences. First, benefits to patients are unknown and may be negligible (as in the case of peramivir), in which case expanded access undermines physicians' attempts to practice evidence-based medicine. Second, medications such as hydroxychloroquine have well-documented risks; subjecting patients to these risks would be unjustifiable in the absence of meaningful clinical benefit. Third, distributing unproven drugs under expanded access or EUAs may detract from the resources needed to carry out clinical trials, including the patient base and necessary funds. Since key outcome data are often not collected outside a trial, this redirection of resources will hamper our ability to quickly determine whether these drugs are truly safe and effective.

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[1] Kim AHJ, Sparks JA, Liew JW, et al. "A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID–19." *Ann Intern Med* 2020 March 30 (Epub ahead of print).

[2] Pavia AT. "Editorial commentary: what did we learn from the emergency use authorization of peramivir in 2009?" *Clin Infect Dis* 2012;55:16–18.

[3] Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. "Regulatory review of novel therapeutics—comparison of three regulatory agencies." *N Engl J Med* 2012;366:2284–2293.

[4] Darrow JJ, Avorn J, Kesselheim AS. "FDA approval and regulation of pharmaceuticals, 1983–2018." *JAMA* 2020;323:164–176.

Finally, with drugs that are already marketed for other conditions, widespread off-label use can limit access for patients who need them for their established use. After Trump promoted hydroxychloroquine, prescribing of the drug increased rapidly, leading to substantial shortages affecting patients taking it for rheumatoid arthritis or lupus—indications for which it has been proven effective.

During a pandemic that is causing morbidity and mortality to grow exponentially, there is an understandable temptation to make unproven therapies widely available and not wait for rigorous clinical trial data. However, well-conducted randomized, controlled trials in these acutely ill patients can actually be carried out quite rapidly. Thousands of new patients with COVID–19 present for care each day, and many can be (and are) quickly enrolled in pragmatic clinical trials. The most relevant clinical outcomes for evaluating these drugs—including death, hospitalization, number of days spent in intensive care, and need for a ventilator—are readily assessed and available within days or weeks.

At least 25 drugs are under investigation for use in COVID–19, with 10 in active clinical trials. The first published major randomized, controlled trial of an antiviral drug combination (lopinavir-ritonavir) began enrolling patients in China just a week after the virus had been identified.[5] Contrary to expectations, its results were negative, providing important clinical guidance.

If data emerge showing that any regimen is truly effective in treating COVID–19, the FDA should be able to review those data and provide an approval decision within days or weeks. The agency has already established a Coronavirus Treatment Acceleration Program to assist manufacturers in navigating administrative requirements and to expedite the review process.

Adequate clinical trials will soon confirm or refute the usefulness of several candidate drugs in treating COVID–19. But the weeks leading up to provision of that evidence reveal a great deal about threats to our approach to evaluating medications. Issues such as inadequate trial design, overreaching public declarations, and widespread use of unproven treatments will continue to present themselves during this pandemic and beyond.

Rigorous premarketing evaluation of drugs' safety and effectiveness in randomized, controlled trials remains our primary tool for protecting the public from drugs that are ineffective, unsafe, or both. It is a false dichotomy to suggest that we must choose between rapid deployment of treatments and adequate scientific scrutiny. For the COVID–19 pandemic and other pressing medical challenges, the health of individual patients and the public at large will be best served by remaining true to our time-tested approach to clinical trial evidence and drug evaluation, rather than cutting corners and resorting to appealing yet risky quick fixes. The pandemic will inevitably leave considerable morbidity, mortality, and loss in its wake. Damage to the country's medication-assessment process—and the public's respect for it—should not be part of its legacy.

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[5] Cao B, Wang Y, Wen D, et al. "A trial of lopinavir-ritonavir in adults hospitalized with severe COVID–19." *N Engl J Med* 2020;382:1787–1799.

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The Association for Accessible Medicines (AAM) is pleased to submit the following statement for the record for the Senate Finance Committee's hearing on "COVID–19 and Beyond: Oversight of the FDA's Foreign Manufacturing Inspection Process." As the nation's leading trade association for the developers, manufacturers and distributors of FDA-approved generic and biosimilar prescription medicines, AAM and our members are committed to the secure and consistent supply of critical medicines to improve the health of America's patients and as a critical tool in the effort to lower prescription drug costs.

Introduction

As the Finance Committee examines the pharmaceutical supply chain, we wish to stress three points:

- The generic drug industry currently manufactures approximately 70 billion doses in the U.S.;
- AAM and its members strongly support the Generic Drug User Fee Amendments (GDUFA) program enacted in 2012 and reauthorized in 2017, which has provided the resources for FDA to dramatically increase its capacity to inspect facilities, both domestic and foreign, that support an application; and
- Building on today's U.S.-based production and FDA's oversight, AAM and its members have released the "Blueprint to Enhance the Security of the U.S. Pharmaceutical Supply Chain" to provide Congress and the Administration with recommendations on how to further strengthen the pharmaceutical supply chain and enhance the U.S. manufacturing of essential medicines.

The COVID–19 pandemic reminds us of the incredible value offered by the generic and biosimilar industry, the benefits of a resilient and redundant global supply chain, and industry's daily commitment to manufacturing safe, effective and high-quality medicines.

AAM's members have experienced substantially increased demand for certain medicines that has far exceeded historical trends,[1] navigated export restrictions on active pharmaceutical ingredients (API) and finished dose (FD) generic medicines,[2] rerouted the delivery of medicine as air travel was significantly curtailed around the globe,[3] and absorbed much of the increased costs charged for the transportation of medical products to ensure that America's patients are able to access critically needed medicines during the coronavirus pandemic.[4] In response, AAM's member companies have stepped up to meet these challenges.[5]

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[1] Ellen Gabler and Michael Keller, "Prescriptions Surged as Trump Praised Drugs in Coronavirus Fight," *New York Times,* April 25, 2020, updated May 19, 2020.

[2] Rajesh Roy, "India Again Allows Export of Antimalarial Drug Touted for Coronavirus," *Wall Street Journal,* April 7, 2020.

[3] Ian Duncan, "Drug Industry Warns That Cuts to Passenger Airline Service Have Put Medical Supplies at Risk," *Washington Post,* May 2, 2020.

[4] AAM Survey of Biosimilar and Generic Drug Manufacturers, "Pharmaceutical Shipping Costs Spike in Response to Global COVID–19 Pandemic," April 30, 2020.

[5] AAM, "Generics and Biosimilars Industry Supply Chain and Response to COVID–19," April 10, 2020.

Implementation of the CARES Act Will Enhance FDA's Regulation of the Global Supply Chain

We understand why the Finance Committee would raise questions about recent reports that may paint a distorted picture of a global supply chain that is overly reliant on China and other countries for API. Our statement clarifies and provides more accurate analysis of where API and finished dosage form (FDF) facilities are located, according to testimony provided by FDA to Congress last year. Moreover, Congress took important action as part of the Coronavirus Aid, Relief, and Economic Security (CARES) Act (H.R. 748) enacted in March. The CARES Act includes several important steps intended to help strengthen the pharmaceutical supply chain. Specifically, the CARES Act:

- Increases the transparency of the pharmaceutical supply chain by providing FDA with additional information on potential disruptions in the supply chain, on manufacturers' contingency plans to ensure continued supply and on the volume of medicines manufactured (Section 3112);
- Stresses the importance of air transportation in maintaining well-functioning pharmaceutical supply chains (Section 4005);
- Evaluates U.S. dependence on overseas manufacturing with a forthcoming report from the National Academies (Section 3101); and
- Strengthens the national stockpile to ensure access to drugs, vaccines and other biological productions (Section 3102).

We believe these provisions will help answer some of the questions raised once implemented and will serve to further inform policymakers about the economic realities of the generic and biosimilar markets. In this statement, we provide additional information on the role of generics and biosimilars in improving patient health, how more affordable treatments enhance patient access, details FDA's oversight role and inspections process, and outline our industry's robust commitment to quality.

Generics and Biosimilars Are Integral to Patient Health

Generic medicines play an integral role in health care and enhance patient access to life-saving treatments. The expiration or invalidation of patents and the resulting introduction of multiple generic and biosimilar manufacturers competing against each other on price result in significant savings for patients and the health care system. Over the last 10 years, manufacturers of generic medicines have delivered savings of nearly $2 trillion—including $293 billion in 2018—to patients and the health care system.[6]

Biosimilar medicines represent another critical step forward in reducing high drug prices. Biosimilars are safe, effective and more affordable versions of costly brand biologics. By the year 2025, over 70 percent of drug approvals are expected to be biological products.[7] Experts estimate that FDA-approved biosimilars could save more than $54 billion over the next 10 years.[8] In doing so, biosimilars will mean greater access to lifesaving cures for an estimated 1.2 million patients.[9]

The introduction of generic and biosimilar competition significantly reduces the price of medicine, and patients benefit from greater, more affordable access to FDA-approved drugs. Experience shows prescription drug prices decline by more than half the first-year generics enter the market.[10] Early experience with the nascent biosimilars market in the U.S. shows that these more affordable alternatives are also providing value and savings to patients, on average priced 40 percent lower than their branded biologic counterparts.[11]

However, one must also consider the underlying economic realities of the generic and biosimilar markets. Prices for generic drugs are plummeting—falling for 40 of the last 45 months—and creating a market in which many drugs are simply and increasingly not economical to produce.[12] The biosimilars market is still developing with 17 of the 26 FDA-approved biosimilars launched with only a handful regularly

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[6] AAM, "The Case for Competition: 2019 Generic Drug and Biosimilars Access and Savings in the U.S. Report," September 2019.

[7] U.S. Pharmacist, "Biosimilars: Current Approvals and Pipeline Agents," October 2016.

[8] RAND, "Biosimilars Cost Savings in the United States," October 2017.

[9] The Biosimilars Council, "Biosimilars in the United States: Providing More Patients Greater Access to Lifesaving Medicines," August 2017.

[10] IMS Institute for Healthcare Informatics, "Price Declines After Branded Medicines Lose Exclusivity in the U.S.," January 2016.

[11] AAM analysis of IQVIA WAC Data, December 2018.

[12] Morgan Stanley, April 2020.

prescribed.[13] Biosimilar manufacturers are increasingly looking to provide Europe's patients with access first, rather than the U.S., due to the barriers to competition and a policy environment that inadequately supports their uptake and use domestically.[14]

Setting the Record Straight on the Global Production of Medicines and the FDA's Gold Standard of Safety

In testimony before the House Energy and Commerce's Subcommittee on Oversight and Investigations on December 10, 2019, Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research at FDA, provided a detailed breakdown of where API and FDF of prescription drugs—inclusive of brand-name and generic medicines—are located.[15] The U.S. is home to 47 percent of FDF facilities and 28 percent of API facilities as of August 2019, according to the FDA.[16]

As depicted in Figures 1 and 2 from FDA's testimony, and included below, the number of FDF and API facilities regulated by FDA is as follows:

FDF Facilities, By Geographic Region

- U.S.—47 percent
- Europe—18 percent
- India—11 percent
- China—7 percent
- Rest of World—13 percent

API Facilities, By Geographic Region

- U.S.—28 percent
- Europe—26 percent
- India—18 percent
- China—13 percent
- Rest of World—13 percent

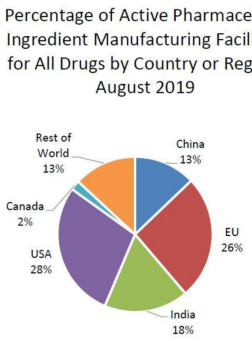

Figure 1: For all FDA-regulated drugs, 28 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

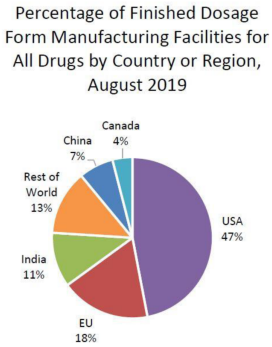

Figure 2: For all FDA-regulated drugs, 47 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

Globalization of the supply chain—a market reality for brand-name drug companies and generic and biosimilar manufacturers—is often mentioned as a matter of concern, but the record should in fact bolster confidence in the system. The U.S. has one of the safest drug supply chains in the world.

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[13] Biosimilars Council, "FDA Biosimilars Approvals," April 2020.

[14] Biosimilars Council, "Failure to Launch: Barriers to Biosimilar Market Adoption," September 2019.

[15] Janet Woodcock, M.D., Director of CDER, FDA, testimony, Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, hearing on "Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program," December 10, 2019.

[16] *Ibid.*

FDA's Oversight of the Pharmaceutical Supply Chain

FDA ensures all pharmaceuticals meet the same high-quality standards regardless of where brand-name drugs, biologics, generics and biosimilars are manufactured. All pharmaceuticals, whether generic or brand, must be manufactured in accordance with rigorous regulatory standards that require high levels of diligence and accompanying documentation.[17] FDA and other governmental requirements cover each of the following areas:

- Acquisition of raw materials and drug packaging components, including auditing the manufacturers and suppliers of critical ingredients;[18]
- Testing of active ingredients using qualified equipment and validated methods;[19]
- Constructing and maintaining manufacturing equipment and facilities that have been constructed and maintained to provide sanitary conditions and to protect against contamination;[20]
- Appropriate and documented training of manufacturing personnel;[21]
- Validation of manufacturing processes to ensure that they consistently produce safe, effective and uniform medicine;[22]
- Thorough contemporaneous documentation of each manufacturing step, with oversight by an employee other than the operator for critical manufacturing steps;[23]
- Taking samples of prescription drugs during the manufacturing process at predetermined intervals, and testing the samples for potency and, where appropriate, sterility;[24]
- Maintaining rigid controls over labels placed on drug containers, to ensure the correct labels are placed on every package;[25]
- Thorough testing of prescription drugs before packaging to ensure that they are free of microbial contamination or other defects, and that they meet tight specifications for uniformity, potency and lack of impurities;[26]
- Retention of samples of all manufactured batches of prescription drugs;[27]
- Routine stability testing to ensure that prescription drugs, including biologics, will remain safe and effective for the duration of their shelf lives;[28]
- Release of each batch of prescription drugs for distribution only upon review of all batch records and testing data by a quality unity that is independent of manufacturing personnel;[29]
- Continuous oversight by management and regular audits by an independent quality unit of the manufacturer or outside consultants;[30]
- Rigorous documentation of every step in the storage and distribution of manufactured prescription drugs;[31] and
- Prompt reporting to FDA and thorough investigation of any complaints about distributed medicines, or any reports that the prescription drugs may have failed to remain safe and effective.[32]

When FDA finds any deviation from the strict standards of production, FDA can take swift action. Potential actions include: mass recall of products; issuing public Warning Letters; imposing import alerts and barring the admission into the U.S. of violative API or FDF; seizing violative medicines; seeking court orders suspending distribution of drug products until FDA approves resumption of operations; and pur-

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[17] 21 Code of Federal Regulations Parts 210, 211, 600–680; Inspection of Biological Drug Products, FDA Compliance Program Guidance Manual, Chapter—45 Biological Drug Products, Section 7345.848.
[18] 21 CFR § 211.182.
[19] 21 CFR § 211.84.
[20] 21 CFR § 211.42, § 211.56 (facilities), § 211.65, § 211.67 (equipment).
[21] 21 CFR § 211.25.
[22] 21 CFR § 211.100.
[23] *Ibid.,* 21 CFR § 211.101(c), § 211.180(a), § 211.186, § 211.188(b).
[24] 21 CFR § 211.110.
[25] 21 CFR § 211.122, § 211.125, § 211.130, § 211.134.
[26] 21 CFR § 211.113, § 211.165, § 211.194.
[27] 21 CFR § 211.170(b).
[28] 21 CFR § 211.165.
[29] 21 CFR § 211.22, § 211.142, § 211.167, § 211.192.
[30] 21 CFR § 211.180(e), (f).
[31] 21 CFR § 211.150(b), § 211.196; Drug Supply Chain Security Act, Title II of the Drug Quality and Security Act of 2013.
[32] 21 CFR § 211.198.

suing criminal prosecution of individuals and companies when necessary.[33] FDA does not hesitate to exercise these powers, taking action not only when prescription drugs are determined to be defective, but when FDA believes that the system of manufacturing is inadequate to guarantee that all prescription drugs are safe and effective.

GDUFA, originally enacted in 2012 and then reauthorized in 2017, included a $4 billion commitment from the generic drug industry.[34] One primary reason the generic drug industry supported the user fee program for generic drugs was the imbalance between the frequency of inspections for domestic manufacturers and foreign manufacturers, especially those located in China and India. Statistics at the time showed that large generic manufacturers located in the U.S. could expect to be inspected by FDA once every two to three years. In contrast, major suppliers of prescription drugs based in China and India were inspected, on average, less than once every 10 years.

GDUFA has significantly increased and continues to augment the funding of FDA's generic drug review and inspection programs. GDUFA substantially increased FDA's review capacity and the frequency of inspections. FDA hired nearly 1,200 employees to strengthen oversight under GDUFA implementation and 338 additional employees were added as a result of GDUFA II.[35]

Indeed, GDUFA fees and the foreign drug manufacturer inspections by FDA that the fees enable have dramatically changed where FDA has focused its inspection and enforcement efforts. Until 2012, the majority of FDA Warning Letters relating to manufacturing violations issued to mainstream drug manufacturers were based on inspections at facilities located in the U.S. In 2011, for instance, 45 percent of FDA Warning Letters for drug manufacturing violations were based on inspections of facilities outside of the U.S. More recent data, for 2016, shows 98 percent of FDA Warning Letters were issued to facilities located outside of the U.S.[36] The increase in enforcement actions against drug manufacturing facilities located outside of the U.S. is directly attributable to an increase in the number of FDA inspections. However, it is important to remember that most manufacturers that are inspected are found to be fully compliant with the regulations.[37]

FDA utilizes a risk-based inspection strategy, established under Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA), to maintain a robust inspections footprint around the world. FDA has established offices in China and India and uses GDUFA funding to support those offices. FDA's global inspection efforts are prioritized and focused on facilities in a way to prevent, uncover and combat data integrity issues and manufacturing problems. Using a risk-based site selection surveillance inspection model, FDA prioritizes domestic and foreign inspections based on multiple factors carefully selected to appropriately target the agency's resources.

In fiscal year 2017, FDA conducted 935 inspections of generic drug manufacturing facilities in the U.S. and around the world.[38] This includes 547 international inspections and 388 domestic inspections. Moreover, the level of inspections increased between fiscal year 2013 and fiscal year 2017 (five years) from a total of 721 inspections. As former FDA Commissioner Scott Gottlieb, M.D., noted at the time, "We expect these trends to continue due to resources from GDUFA II."[39]

AAM and its members remain committed to ensuring FDA continues to have the resources to perform thorough inspections of facilities that manufacture all medicines approved in the U.S. We are pleased that the number of FDA's foreign inspections continue to rise, in no small part based on funding provided by AAM's member companies through GDUFA and the Biosimilars User Fee Act (BsUFA).

AAM's Blueprint to Strengthen the U.S. Pharmaceutical Supply Chain

As part of the industry's ongoing commitment to patient access, AAM released a six-element framework that lays out concrete actions to ensure that U.S. patients and

[33] FDA Public Databases on Drug Recalls, Warning Letters, and Import Alerts; Ned Sharpless, M.D., "Expanding Criminal Enforcement Operations Globally to Protect Public Health," FDA, October 2019.
[34] FDA, Five-Year Financial Plan for the Generic Drug User Fee Amendments, 2018.
[35] Kathleen Uhl, Director of Office for Generic Drugs, Presentation: Director's Update, February 2016.
[36] Independent review of FDA's public database of Warning Letters.
[37] FDA, "Facts About the Current Good Manufacturing Practices (CGMPs)," June 2018.
[38] FDA, FY2017 Performance Report to Congress for GDUFA, May 2018.
[39] Scott Gottlieb, tweet on FY 2013–17 Inspectional Data, January 2019.

the U.S. health care system have access to a secure and consistent supply of critical medicines.[40] AAM's "Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain" builds upon the existing generic drug supply chain in the U.S., which produces approximately 70 billion doses annually and provides more than 36,000 jobs in nearly 150 manufacturing facilities across the country. AAM and its members seek to provide solutions that will enable expanded investment in the manufacturing of medicines domestically.[41] Creating the conditions that support and encourage this investment are critical to ensuring the most critical medicines—those most essential to our country's health and security—are manufactured in the U.S. In order to establish this environment, AAM's Blueprint recommends the following:

- Identify the list of medicines most critical for U.S.-based manufacturing;
- Provide new grant and tax incentives to secure the U.S. supply chain;
- Supply the Strategic National Stockpile, the U.S. Department of Veterans Affairs, and other agencies with essential medicines on a long-term basis;
- Reduce regulatory inefficiencies to streamline the federal approval for U.S.-based facilities to manufacture medicines; and,
- Promote a global, cooperative approach to diversifying the supply chain.

The Blueprint includes actionable short-term steps to expedite more U.S.-based production of essential medicines, while putting in place a series of incentives to enhance the security of the U.S. pharmaceutical supply chain. Given modern manufacturing facilities can take 5–7 years and cost up to $1 billion to build, a long-term, consistent commitment from the federal government is critical to building an expanded generic manufacturing base in the U.S.

Importantly, the Blueprint offers a targeted approach to addressing potential vulnerabilities in the U.S. pharmaceutical supply chain, while building on the existing capacity in the U.S. and what is widely recognized as one of the safest drug supply chains in the world. Through its rigorous approval process, manufacturing regulations and continuous inspections of manufacturing facilities, FDA ensures that "medicines at all levels of the supply chain, from active pharmaceutical ingredients (API) to the finished product sold to consumers at the pharmacy counter are safe, effective and high quality."[42] This is why every administration of both parties and, including the current Secretary of Health and Human Services Alex Azar, are publicly on record assuring America's patients that FDA would not approve generics if they were not safe and effective treatments.[43]

Our Industry's Commitment to Quality and Patient Safety

Patient safety is the number one priority for AAM and its member companies. AAM's members adhere to a code of business ethics and the "Safety of Medicines" is its first principle.[44] Every AAM member company pledges to "conform to high standards of quality, safety and efficacy as determined by regulatory authorities in each economy in which they operate."[45] This commitment to quality, safety and efficacy applies regardless of where medicines are manufactured.

Patients should know and be confident in the quality of the generic medicines prescribed and consumed. Generics and biosimilars are just as safe and effective as their brand-name drug counterparts. Independent research consistently demonstrates the clinical equivalence of generic medicines compared to the brand-name drug.[46]

Patients can trust the safety and effectiveness of generic medicines. And it is important that patients take their medicines as prescribed by their physicians. As Secretary Azar has previously stated:

> Every single drug I take is a generic. They are exact copies. They wouldn't get approved by the FDA if they weren't.[47]

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[40] AAM, "A Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain," April 30, 2020.

[41] Based on a 2016 survey of AAM's member companies.

[42] Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's CDER Janet Woodcock, M.D., "FDA's continuing efforts to maintain its strong oversight of generic drug quality issues domestically and abroad," February 2019.

[43] Alaric DeArment, "FDA commissioner praises generic industry's efforts on quality, shortages, follow-on biologics in GPhA speech," *Drug Store News,* February 2013.

[44] AAM, Code of Business Ethics, March 2018.

[45] *Ibid.*

[46] FDA, Generic Drugs: Questions and Answers, June 2018.

[47] Secretary Azar, interview on Fox and Friends, October 2019.

While it is not always possible to combat all of the misinformation that exists, we encourage lawmakers to avoid, to the extent possible, repeating and sometimes promoting inaccurate information on quality that can potentially result in placing patients in harm's way by way of promoting non-compliance of their prescribed medication regimen. As FDA has emphasized, not taking one's medicine as prescribed by a doctor or as instructed by a pharmacist, due to unsubstantiated claims on quality, could have the undesired effect of exacerbating a patient's illness or disease, and lead to worse health outcomes.

Moreover, and as described previously, FDA provides regulatory oversight of the manufacturing of generic and biosimilar medicines. Manufacturing facilities located overseas, as well as in the U.S., are routinely inspected by FDA to ensure the medicines are of the highest quality for patients. A standardized, transparent and dynamic system is in place and is working for doctors, pharmacists and patients.

Quality Is Standard

Exacting standards ensure the reliability of the medicines we take. These standards make it possible for us to trust that a pill dispensed from a pharmacy in Oregon in the spring will match, in every way that matters, a pill picked up at a drug store counter the following winter in Miami.

Dr. Jeremy Greene, professor of medicine and the history of medicine at Johns Hopkins University and author of "Generic: The Unbranding of Modern Medicine," explained in a recent interview with United States Pharmacopeia (USP):

> There's a mutual interest among manufacturers, whether they are brands or generics, for establishing and disseminating a public standard that helps us determine if a drug is what it says it is.[48]

The various stakeholders—health care professionals, industry, and government—that keep our drug supply safe agree upon the standards, and USP publishes the standards and the methods that manufacturers and regulators can employ to demonstrate that medicines are what they should be. These standards apply to a drug's molecular structure, and to the amount of active and inactive ingredients it contains to ensure a drug's efficacy and safety.

USP strives for comprehensive standards, which is no small task. According to its latest annual report, more than 3,700 reference standards and more than 6,700 documentary standards have been issued.[49] USP's collaborative work with FDA to set drug quality standards for nearly 80 years has made drugs marketed in the U.S. the gold standard worldwide for safety and quality.

Transparency Enhances Quality

All of the links along the supply chain have an obligation to be open and transparent about issues related to safety and quality. This is how the system secures the accountability necessary to earn and retain the trust of the medical profession and, ultimately, the patients.

FDA has a robust around-the-clock program for inspecting pharmaceutical manufacturing facilities worldwide. The Office of Regulatory Affairs (ORA) conducts assessments, inspections, research and surveillance of pharmaceutical manufacturing facilities. AAM's member company manufacturing facilities, all over the world, must be ready for FDA inspection whenever they are operating, 365 days a year. Our member companies have established interlocking processes and procedures to ensure the quality and integrity of the medicines manufactured in these facilities.

Generic manufacturers not only readily comply with inspections audits; they also fund this oversight through GDUFA, which supports FDA staffing and best practices in protecting public health and accelerating innovation. These fees total nearly $500 million annually.[50] Foreign as well as domestic companies identify and register all facilities involved in the manufacturing of generics and their active ingredients. BsUFA operates on similar principles.

Reports from the public, health care professionals and the industry of potentially defective drug products help FDA identify sites for inspection or investigation. Most

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[48] Jeremy Greene, "Similarity and difference in the world of drugs," USP, accessed October 2019.
[49] USP Annual Report, "USP by the numbers: Fiscal year 2019," accessed October 2019.
[50] FDA, "GDUFA II Fee Structure Summary," accessed October 2019.

companies that are inspected are found to be fully compliant with the regulations.[51] In addition, Post-marketing Surveillance Programs are in place to identify adverse reactions that did not appear during the drug approval process.

Critics may point to product recalls to draw attention to issues in the supply chain, but we believe the rarity of these events demonstrates the system's effectiveness. Indeed, recalls are occasionally required not when a flaw or defect is identified in a medicine, but rather when FDA believes that there is inadequate assurance of adequate quality systems at a plant because manufacturing does not strictly comply with the rigorous regulatory requirements. We would also note that while 90 percent of prescriptions filled in the U.S. are generic medicines, generic drugs account for only 56 percent of any prescription drug recalls.[52] Brand products on the other hand account for only 10 percent of prescriptions filled, but 44 percent of the total recalls.[53]

When an issue is discovered, the proper mechanisms are activated, and industry works with FDA to appropriately address it. In the unlikely event that flawed medication does reach a patient, we should take comfort that all medicines can be traced to the manufacturer. The manufacturer of the product immediately notifies stakeholders in the supply chain, and then pharmacists or physicians reach out to notify patients and to determine alternative prescription options. Obviously, these recalls are widely publicized; transparency contributes to quality.

The Global Supply Chain Is Dynamic

FDA and the industry are constantly adapting to manufacturing innovations. Current Good Manufacturing Practice (cGMP) regulations address methods, facilities and controls used in manufacturing, processing and packaging. The globalization of the supply chain, which is a fact of life for brand, generic and biosimilar drugs, is often mentioned as a matter of concern, but in fact, the record bolsters confidence in the system. While it is true that so-called fake drugs circulate in developing nations through mail-order and online pharmacies, U.S. regulations, guidance and legislation are in place to minimize the possibility that they could reach America's patients.[54] Further, the only additional method of preventing counterfeit or unapproved medications from reaching the U.S. market would be to rigorously examine and test all incoming parcels and packages that could contain medications—a measure that AAM would support. Only a tiny fraction of incoming parcels and packages are currently examined.

These factors ensure patients can take their medications with confidence. Dr. Michael Kopcha, Director of the Office of Pharmaceutical Quality (OPQ) in FDA's Center for Drug Evaluation and Research (CDER), may have put it best when he said:

> The quality of our drug supply is better than ever before. There is no difference in the quality of drugs based only on where they are made.[55]

Conclusion

Patients can and should trust in the safety and effectiveness of generic and biosimilar medicines. FDA ensures all pharmaceuticals meet the same high-quality standards regardless of where medicines are manufactured. Globalization of the supply chain—a market reality for brand-name drug companies and generic and biosimilar manufacturers—is often mentioned as a matter of concern, but the record should in fact bolster confidence in the system. The U.S. has one of the safest drug supply chains in the world. And this is the result of the daily commitment to quality from AAM's member companies and FDA oversight. With that said, there are steps that the federal government can take to enhance the U.S.-based production of critical medicines and we look forward to working with the Finance Committee and its members to advance the recommendations outlined in the "Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain."

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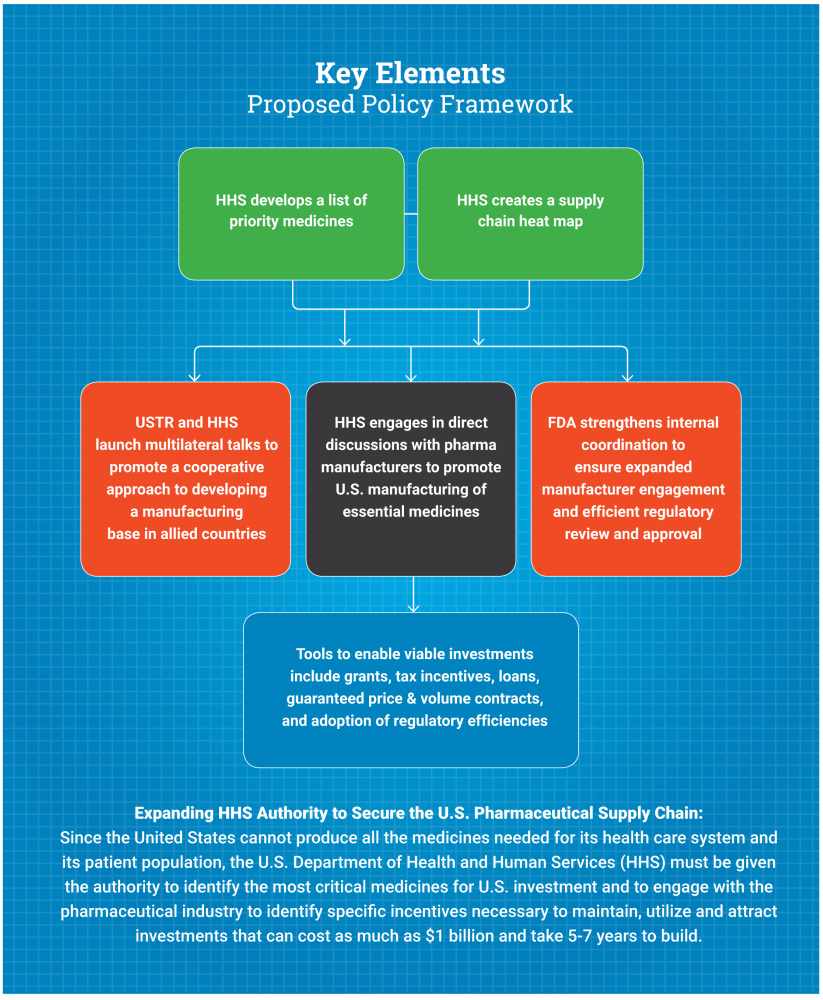
[51] FDA, "Facts About the Current Good Manufacturing Practices (CGMPs)," June 2018.
[52] FDA database, "Recalls, Market Withdrawals, and Safety Alerts," 2011–18.
[53] *Ibid.*
[54] Fight the Fakes, "US FDA Gives Tips on Spotting Fake Medicines," June 2014.
[55] Michael Kopcha, "CDER Conversation: Assuring Drug Quality Around the Globe," FDA, May 2019.

A Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain

INTRODUCTION

A closely connected, diverse, high-quality and resilient pharmaceutical supply chain based in the United States and in U.S. allied countries (such as Canada, Europe, India, Israel, Japan, Jordan and Mexico) is the best means to ensure that U.S. patients and the U.S. health care system have access to a secure and consistent supply of critical pharmaceuticals. The United States already plays an important role in this supply chain, with generic companies providing more than 36,000 jobs at nearly 150 facilities, and manufacturing more than 70 billion doses of prescription medicines annually.[1]

With strategic support from the U.S. government, the economic footprint of the generic drug industry in the U.S. can expand even more, leading to increased national security, a stronger, more redundant supply chain for key pharmaceuticals or their components and an expanded employment base.



[1] Based on a 2016 survey of Association for Accessible Medicines' member companies.

A. IDENTIFYING THE LIST OF MEDICINES MOST CRITICAL FOR U.S. MANUFACTURING

- **List of Essential Medicines.** Within 180 days of enactment, the Secretary of HHS shall establish a list of essential medicines for the United States. Essential medicines are defined as the active pharmaceutical ingredient (API) and finished dosage form (FD). The list of essential medicines shall include medicines deemed most critical to the U.S. health care system, vital during a secretary-designated public health emergency, and/or those that, if shortages occurred, could impact U.S. national security. In developing the list, the secretary shall consult with the U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH) and other public health agencies, as well as the Secretary of Defense and Secretary of State. The list shall be subject to a 60-day public comment period.
- **Assessment of Supply Chain.** Within one year of enactment, the Secretary of HHS shall prepare an assessment of the global supply chain's ability to source and manufacture the medicines on the list of essential medicines.[2] The assessment shall identify the location and number of facilities involved in the production of FD and API. The secretary shall consider several factors in preparing the assessment, including but not limited to the number of manufacturers of each FD and API; the number of manufacturers with approved Abbreviated New Drug Applications (ANDA); the market shares for manufacturers of each FD and API; the volume of FD and API manufactured at each facility; the extent of supply redundancy for each FD and API; and the geographic location of FD and API facilities. Information provided to HHS as part of the assessment shall be confidential and not subject to public disclosure due to its proprietary nature and potential to impact the market. The Secretary of HHS shall prepare and submit a report providing recommendations to Congress on how to strengthen the supply chain to ensure sustainable U.S. patient access to all essential medicines.
- **Designation of "High Priority" Essential Medicines.** From the list of essential medicines, and informed by the assessment of the supply chain, the Secretary of HHS shall publish a list of "high priority" essential medicines for the purpose of ensuring U.S. production and supply of those medicines. The secretary shall update the list annually and may designate additional medicines—including those not previously deemed essential—as "high priority" during a secretary-designated public health emergency. The list, and any updates, shall be subject to a 30-day public comment period.

B. INCENTIVES TO SECURE THE U.S. PHARMACEUTICAL SUPPLY CHAIN

Within six months of the completion of the list of "high priority" medicines, HHS, acting through the Office of the Assistant Secretary for Preparedness and Response (ASPR), will seek new and specific proposals from pharmaceutical manufacturers to determine how individual companies can help secure the U.S. harmaceutical manufacturing base for priority medicines. Proposals would include the list of specific FDs and APIs the company proposes manufacturing in the United States, and the specific type of incentives necessary to make the facilities economically viable. HHS would be authorized to make:

- **Long-Term Price and Volume Guaranteed Contracts.** Guaranteed volume and price agreements are essential to ensuring the viability of U.S.-based generic manufacturing for "high priority" medicines and to inoculate those investments against low-priced imports of the same medicine. When engaging with the industry, however, HHS must encourage multiple suppliers in the market and ensure, whenever possible, that no one company supplies the entire market (this protects against supply disruptions). The price and volume agreements would provide purchase guarantees that could be spread across the Strategic

[2] The Coronavirus Aid, Relief, and Economic Security (CARES) Act (H.R. 748) included several important steps intended to help strengthen the pharmaceutical supply chain. The CARES Act increases the transparency of the pharmaceutical supply chain by providing FDA with additional information on potential disruptions in the supply chain, on manufacturers' contingency plans to ensure continued supply and on the volume of medicines manufactured (Section 3112); stresses the importance of air transportation in maintaining well-functioning pharmaceutical supply chains (Section 4005); evaluates U.S. dependence on overseas manufacturing with a forthcoming report from the National Academies (Section 3101); and strengthens the national stockpile to ensure access to drugs, vaccines and other biological products (Section 3102). The policies outlined in this paper build on and enhance these provisions.

National Stockpile (SNS) and all federal agencies that procure medicines through the Federal Supply Schedule. For the SNS, HHS may take possession of such purchases or may pay manufacturers an inventory management fee to produce and maintain the specified quantity on behalf of the SNS. Specific volume and price levels would be negotiated on a company-by-company basis.

- **Grants.** HHS shall provide grants to support construction, alteration or renovation of facilities for the U.S.-based manufacture of medicines included on the high priority medicines list. Grants shall also be provided to pharmaceutical manufacturers to relocate production facilities from outside of the United States back to the United States to cover expenses in moving production and include funds to offset the cost of building new factories and research centers. Such grants shall be available only to manufacturers with an approved ANDA or authorized generic or to external/contract manufacturers of approved ANDAs or authorized generics. To support a diverse and reliable supply, such grants shall be available to multiple manufacturers of the same medicine. Grants will be administered by HHS/Biomedical Advanced Research and Development Authority (BARDA).

C. OTHER NECESSARY ELEMENTS TO SUPPORT AN EXPANDED U.S. PHARMACEUTICAL ECONOMIC FOOTPRINT

Certain additional measures will be necessary to support the economic viability of a U.S.-based pharmaceutical investment. The following elements will not be negotiated at an individual company level, like those listed above, but will instead be adopted for the entirety of the U.S. generics or biosimilars pharmaceutical manufacturing base:

- **Tax Incentives.** New tax incentives must be passed that promote U.S. pharmaceutical companies relocating foreign manufacturing back to the United States, build new greenfield sites, refurbish already existing manufacturing facilities and/or repurpose existing production lines to focus on pharmaceuticals that appear on HHS's list of "high priority" medicines.
  - ⩾ Manufacturers of medicines designated as "high priority" medicines shall be eligible for a tax deduction during whichever of the two periods is longer: throughout the period the medicine is deemed "high priority" or during the initial period that company has agreed with HHS to supply from its expanded investment. Specific tax incentives that will facilitate the onshoring of U.S. pharmaceutical manufacturing include:
  - ⩾ A dollar-for-dollar credit against federal taxes to pharmaceutical manufacturers for 50% of wages, investments and purchases made for manufacturing medications on the priority medicines list in the United States.
  - ⩾ A tax reduction modeled after the Section 199 Domestic Production Activities Deduction, which provided a tax deduction of as much as 9% of the company's income attributable to U.S. manufacturing operations.
  - ⩾ Increase the R&D credit rate to 20% for the alternative simplified credit.
  - ⩾ Provide full expensing for the construction of new factories built to move production from overseas to the United States.
- **Regulatory Efficiencies.** To expedite the approval of a facility and all the products to be produced in it the FDA will streamline its regulatory review and approval processes, removing duplicated actions and reducing the time for approvals across the board. The agency will expand cooperation with the manufacturer, working collaboratively to evaluate and approve the facility and the tech transfer processes concurrently, as opposed to waiting until after the facility is built and the equipment is installed/validated.

To accomplish these goals, the FDA will create an internal, intra-agency working group focused on helping to expedite reviews and approvals to onshore pharmaceutical manufacturing. This working group will consist of resources from the Office of Regulatory Affairs; the Office of Pharmaceutical Quality; the Office of Compliance; reviewers from both chemistry and microbiology disciplines; and the Office of Generic Drugs. This working group will focus on reviewing for approval the transfer of production back into either U.S.-approved facilities or newly constructed facilities at new or existing sites, including those utilizing advanced manufacturing technology. This working group will grant meetings with the company to discuss the overall transfer plans. For example:

- ⩾ Inspector(s) and Office of Pharmaceutical Quality staff will make site visit(s) during the construction or validation phase.
- ⩾ The mechanism will be similar to a pre-ANDA meeting—that is, a developmental phase inspection and then a pre-submission inspection.
- ⩾ Microbiology reviewer(s) will conduct site visits.
- ⩾ Decouple submission and inspection. Inspections will be completed within 30 days of request for inspection, regardless of submission.

D. INCREASING U.S. PHARMACEUTICAL SUPPLY CHAIN SECURITY THROUGH GLOBAL COORDINATION

- **The International Pharmaceutical Supply Chain Agreement.** To promote the benefits of a globally diverse supply chain, the United States Trade Representative (USTR), working with HHS, should negotiate a plurilateral agreement with U.S. allies to promote a cooperative approach to securing the U.S. supply chain, ensuring diversity of supply and responding to global health care challenges and natural disasters, without resorting to export controls or other trade barriers. In addition, coordinating the expansion of pharmaceutical manufacturing with U.S. allies will allow for economies of scale and a coordinated approach to global pandemics. Possible signatories would include U.S. allies such as Canada, Europe, India, Israel, Japan, Jordan and Mexico.

Definitions

- "Generic drug" means "any drug that is marketed under an abbreviated new drug application (ANDA) as well an 'authorized generic drug.'"
- "Manufacture" has the meaning set forth in the Buy American Act, 41 U.S.C. §§ 8301 8305: "completion of an article in the form required for use by the government in the United States. For drugs this means readied for use as a medicine for human consumption."

STATEMENT SUBMITTED BY PETER KOLCHINSKY, PH.D.

Safe and inexpensive generic drugs must be made in America

Reliable, high-quality generic drugs are the great value proposition of continued biomedical innovation. They are the ultimate price control on branded drugs and a unique phenomenon in all of healthcare, where nothing else goes generic—not hospitals, not services, not surgery.

Drugs are a manufactured good. The high prices of branded drugs that are necessary to incentivize investment in risky research projects are like a finite set of mortgage payments. Once a mortgage is paid off, America takes ownership of an inexpensive public good. Through their taxes and insurance premiums, our parents paid for branded drugs and passed them on to us as inexpensive generics, as they might a home. Over 90% of all prescriptions in America are for generic drugs [1] and each new drug we invent to improve our standards of care is built on a foundation bought and paid for by past generations.

Consider how easy it is to save money on medicines thanks to generics. If your cholesterol is high, your doctor might prescribe Lipitor, using the brand name of Pfizer's long-generic drug out of habit instead of the generic name "atorvastatin." No worries. Your local pharmacy is permitted by law to fill your prescription using pills made by any FDA-approved manufacturer of atorvastatin. Your pharmacy does the shopping around for you, playing dozens of manufacturers off one another to get the lowest price. You do not have to worry about which company makes your atorvastatin because it is now a commodity; everyone has to make it to standards of bioequivalence defined by the FDA. You probably care more about the manufacturer of your toilet paper than you care about who makes your atorvastatin, presumably because you trust the FDA.

False Economy

But here is the dilemma: It is hard to manufacture drugs reliably, consistently, and to the highest standard. A company has to care about getting the conditions just

[1] *https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1591031020789.*

right and run quality tests at every stage to make sure that the intermediates and final product are exactly as they should be. And while the company that sells a new, branded drug for a high price has a strong profit motive to keep quality high, especially because it has to prove to physicians that this new medicine can be trusted, the same cannot necessarily be said for generic drug companies.

Generic drugs do not always work as well as they should, and globalization has greatly exacerbated this problem. Generic drugs have not earned and do not deserve our blind trust. As transplant surgeons, cardiologists, infectious disease specialists, and psychiatrists have increasingly recognized, a generic version of an essential medicine manufactured by one company can be more or less potent than the original version or a generic manufactured by a different company. A generic might not have the stated amount of an active ingredient. It may contain deadly impurities. In some cases a generic might release a day's worth of drug into the bloodstream all at once; in other cases it might release a drug too slowly. That could mean an infection otherwise easily controlled might instead turn deadly. Blood pressure or high cholesterol could remain unchecked. Or in the case of an organ transplant, a patient taking a generic version of an immunosuppressant might lose their precious new organ to rejection. Not all generics are substandard; some are manufactured correctly and behave the same as branded equivalents. But a growing number of Americans are hesitant to take that risk, and rightly so. Some physicians will only prescribe the branded version of a drug, which often spurs a protracted fight with insurance plans that, like the FDA, consider generics interchangeable with branded drugs and only want to pay for low-cost generics.

One key reason why generics are unreliable is because they are increasingly manufactured overseas, where labor costs and regulatory bars are low. This shift has put factories that manufacture generic drugs practically beyond FDA oversight, which has long been crucial to holding companies accountable for quality standards. In a competitive market that takes quality for granted and prioritizes lower costs, it only takes one bad apple out of a dozen manufacturers to drive all the honest players out of business. As detailed in Katherine Eban's eye-opening book, *Bottle of Lies,* the FDA cannot frequently or adequately inspect the Indian and Chinese manufacturing plants that produce so much of our generic drug supply. Instead of making high-quality medicines, many of these companies circumvent quality regulations through an escalating game of cat-and-mouse with the FDA. Quality testing might be done on samples of Pfizer's own Lipitor, with the resulting data passed off as evidence that these factories' atorvastatin generics work just as well. When companies are run by people without integrity and regulators cannot hold them accountable, the dark side of human nature can flourish. In this case, cutting costs comes at the expense of Americans' health, health worldwide, and the value proposition of biomedical innovation.

I am not suggesting that generic drugs made in America are inherently safer because Americans are more ethical. But what I find somewhat reassuring is that drugs made in America are made on the FDA's home turf where the leading drug regulator in the world can do a more effective job of monitoring quality. In the US, where it can conduct surprise inspections, the FDA issues plenty of warning letters: more than 50 in the last 12 months related to Drug Quality Assurance.[2] But the violations overseas are extreme and all the worse considering that the FDA typically gives several weeks' notice to companies that its inspectors are coming; time used to clean up their operations, or, in some cases, cook their books and coach employees to lie.

An American consumer can hold a local pizza shop accountable for having a dirty bathroom or rancid cheese by writing a bad review and eating elsewhere. But Americans have no such power to demand American-made drugs manufactured under FDA supervision. Just try it.

Look in your medicine cabinet to see which companies make the generic drugs you find there. Odds are good that they are based in India. Now google that company's name together with the term "483" and odds are good you will see that all of these companies committed drug quality violations in the last 12 months. You might ask your doctor or pharmacist to fill your next prescription only with generics made in America. But neither will know how to do that. Your pharmacist is driven by competitive forces to purchase drugs at the lowest possible cost, which increasingly means from overseas manufacturers. If she even has any control over where her

[2] *https://www.fda.gov/drugs/enforcement-activities-fda/warning-letters-and-notice-violation-letters-pharmaceutical-companies.*

pharmacy purchases its atorvastatin, she would be hard-pressed to order from a more expensive US-based manufacturer if her competitors are ordering cheaper Indian-made drugs. Other than writing a prescription for the branded version together with the phrase "Dispense as Written" (to ensure that the pharmacist does not instead dispense a generic), there is nothing your doctor can do. But before you think that prescribing only branded drugs is the solution, consider the fact that this will make most drugs unaffordable. Insurance plans balk at paying brand prices for drugs that have gone generic unless a physician personally fights for an exception, which few have the time to do. The system is fundamentally based on the idea that, for a given drug, all generic versions available in the US are equally safe and effective as one another and the brand. The consumer has no choice!

COVID and Contracting: An Opportunity

Policymakers are considering repatriating America's drug supply chain to avoid future shortages in the context of temporary disruptions caused by COVID–19. But they should think bigger. We should repatriate the American drug supply to restore and preserve the integrity of all generic drugs in America.

That might seem like overkill. Better quality testing of final products, as the pharmacy Valisure has started doing, might suffice in some cases. The trouble is that the kinds of analytical assays done in a lab can only detect some of the defects in a poorly made generic. A drug can be made so that it meets all the lab test specifications, for example, containing the right amount of the active drug and dissolving at the right rate in a beaker, and yet it could still be made in such a way that it acts differently in the human body. That is why the FDA requires that generics companies prove their final products behave very similarly to branded originals in human bioequivalence studies. Once they do, then the process that makes that product must be locked down and the company must document that it remains religiously adherent to that process. The presumption is that, as long as they do, then the final product can be trusted to continue to act as documented in humans. But if generics manufacturers never even made their generic to appropriate specs, lied about their human bioequivalence data, or did not continue to adhere to a process that might have been the right process initially, then it is not a given that subsequent lab tests will detect the failure of their final products to function in patients as intended. Those drugs might still cause dose dumping or not release enough drug at the right point in the gut, resulting in potentially important differences in therapeutic outcome. The bottom line is that generic manufacturing must be done to careful specifications, and Americans need both the quality of the final products and the processes by which they continue to be made to be carefully monitored by a regulator, which in the current framework is the FDA. That can only be done truly reliably in the US (though close, trusting cooperation with certain countries that have similar concerns about low-quality generics is conceivable).

Repatriating the entire competitive generic drug market as it exists today would be counterproductive. We can rebuild the market smarter and more cost-effectively by using long-term procurement contracts: the model we already trust to ensure that America has pandemic flu vaccines and drugs for smallpox. This idea is already gaining traction. Just recently, the federal government awarded a four-year $354 million contract to Phlow,[3] a Virginia-based generic drug manufacturer, to produce certain essential generic medicines. That is the right idea. Now we need to scale that approach many times over with several other companies.

This type of long-term contracting can achieve better quality and might also result in even lower prices than we have today. No doubt competition achieves the lowest profit margins possible under free market principles. But the fixed costs stack up. Even with low profit margins, the total costs of maintaining all those competitors can be high. Instead of trying to get twenty different generics manufacturers to all produce atorvastatin and compete on price, America can negotiate long-term contracts with a smaller number of companies, allowing them to enjoy greater economies of scale and greater profits while America pays less overall. Let's call this "Contractual Genericization."

Say 20 companies end up making generic atorvastatin in the US, competing on price such that no one company makes very much in profit. But each of those companies has to cover its fixed costs without enjoying economies of scale, and the FDA has that many facilities to inspect to ensure high quality. Instead of 20 companies each

[3] *https://www.prnewswire.com/news-releases/phlow-corporation-awarded-354-million-hhsas prbarda-contract-to-manufacture-essential-medicines-in-shortage-301061648.html?tc=eml_clear time*.

having to cover $5M of fixed cost to make a drug ($100M total), we might have two companies serve the US market that each only need to cover $20M of fixed costs ($40M total) due to economies of scale (though each company would still manufacture the drug at two or more locations to mitigate against shortages)—two management teams instead of twenty; fewer, larger factories, instead of many smaller ones. Because of the $60M difference, America could pay those two companies more generously under contract, allowing them to make more profit on an absolute basis, and America would still save money compared to the free-market competitive system. Their greater profitability would give them a strong incentive not to screw up, since failure could mean transfer of the contract (essentially management of high-quality manufacturing facilities) to another company.

Still, there is no doubt that the underlying costs of making drugs in America are higher than doing so elsewhere. Even under long-term procurement contracts, American-made generic drugs might not be less expensive than the ones we get now. But when the drugs we get now are not actually reliable, then whatever low price we pay for them is too high. Better to pay what we must for generic drugs that actually work as intended than pay less for inferior and dangerous products.

The real benefit to Americans of onshoring generic drug manufacturing through contracting would be that we could rely on much tighter quality controls. Not only would generic drugs be American-made, creating American jobs by companies paying taxes in America, but they would be high-quality American made. And with proper funding and incentives, innovation and automation of manufacturing—so-called advanced manufacturing techniques—can help reduce the costs of producing America's drug supply on American soil.

Repatriating generic drug manufacturing does not require that every atom of every drug be made in America. American manufacturers could still purchase commodity chemicals from overseas, provided that they were able to pivot to other sources in case of disruptions and could guarantee quality control of those chemicals before they go into final products. The final steps of packaging exactly the right chemicals in the right combinations at the right pressures in the right formulations with the right coatings has to happen on US soil, where FDA oversight is rigorous.

We can't do this all at once. We need to start by repatriating our drug supply from countries like India and China that have poor track records of adhering to Current Good Manufacturing Practices (cGMP) per FDA requirements. We can leave countries like Ireland (where many drug companies manufacture products for lucrative tax breaks) for last and decide at that time whether it is prudent to cut ourselves off entirely from foreign production.

It is also important that high-quality generics are available globally. As it is, many countries do not trust generic drugs, and rightfully so if one considers that overseas manufacturers have a history of sending the best of t heir tainted goods to the US and selling the worst to Africa, South America, and their own countries. If the US led the way in making high-quality generic drugs, we could end up exporting them to other countries. At the very least, out of pure self-interest if not compassion, America should ensure that everyone in the world gets the proper doses of all antibiotics, since underdosing leads to antimicrobial resistance that could land on our shores.

Generic Drug Contract With America

The framework I am proposing, the Generic Drug Contract with America, would accomplish at least three important goals:

(1) Restore the quality of the American generic drug supply by repatriating most or all generic drug manufacturing to the US where the FDA can keep a close eye on the process.

(2) Protect the American drug supply from disruptions like we have seen due to COVID–19.

(3) Create tens or even hundreds of thousands of high-quality American jobs where they are most needed by tying government contracts for American-made generics to requirements (with federal subsidies) that these companies build their factories in regions and communities that have been hollowed out by globalization.

This model can also help solve another growing problem that Congress has not even begun to contemplate. Some drugs cannot go generic under our existing legal, ethical, and regulatory frameworks. Increasingly, the technologies we are using to treat diseases are complex and some are near-impossible to copy. If we cannot trust ge-

neric manufactures to make atorvastatin reliably, they may never be able to make some of the antibody-drug conjugates and gene therapies that have recently come to market and are on the rise.

The cost of branded drugs that will go generic are worthy, finite mortgage payments that America makes towards a medicine that it will eventually own as a public good (*i.e.,* generic). But the costs of ungenericizable drugs are rent from day one. Companies that sell ungenericizable drugs need never worry about a patent cliff. They need never hustle to invent a new drug to replace lost revenues when older ones face competition. They can just keep making the same thing indefinitely. And while even branded drugs often compete with other branded drugs (for example, there are several statins, several SGLT2 diabetes drugs, and several insulin analogs), having two or three competitors in a class makes for an oligopoly, which still can tacitly collude to extract rents. But there are many cases where only one drug in a class is particularly well suited to some patients and therefore represents a true monopoly. Reliable generics are the true disruptors of oligopolies and monopolies, but that path is not available to certain types of drugs.

The order established by the Hatch-Waxman Act in 1984, which introduced the idea of modern generics that are interchangeable amongst themselves and with the original branded version, did not contemplate biologics or how such drugs could ever go generic. Recombinant insulins launched in the early 1980s, and other biologics only really started coming to market in the 1990s. Yet not until the ACA passed in 2009 with a component called the Biologics Price Competition and Innovation Act (BPCIA) did we get a pathway for biosimilars. Biosimilars are as close to generics for biologics as we can get and yet far from close enough.

The trouble is that the BPCIA was always on weaker ground than Hatch-Waxman in terms of driving cost savings because it is harder to establish interchangeability for a biologic than for a small molecule drug (though that is arguably not as easy as we once thought either). Without interchangeability at the pharmacy level, an insurer cannot just have a pharmacist switch all patients over from a branded biologic to its biosimilar and save a plan money. That is because insurers (and even their employer clients) are addicted to the rebates they have negotiated on branded biologics, which they risk losing by covering cheaper biosimilars of a given drug without the assurance of successfully saving money by having patients actually switch to those biosimilars.[4]

If trying to create a US-based competitive market for generic atorvastatin seems hard and expensive, then doing it for insulins and antibodies will be impossible. For example, Abbvie's Humira, an autoimmune disease antibody, is the most lucrative drug in history. It's been on the market for 18 years, much longer than the 10–15 years typical of more easily genericized small molecule drugs. It does not make sense to wait until five or ten other US companies figure out how to make Humira before America considers its $15B/year mortgage on that drug paid off.

The most reliable manufacturer of any biologic is the company that has been making it for years as a branded drug. The same contracting mechanism that we use to contract with a few companies to make the US generic drug supply can also be used to contract with biopharmaceutical companies to continue to make their biologics at a contracted price once their patents expire—one that is low, but remains profitable. Yes, that is a price control. But it is a fix for the market's failure to achieve the same end through competition.

The Generic Drug Contract with America would achieve a key fourth goal:

(4) Ensure that even conventionally ungenericizable drugs become inexpensive after their patents expire, bringing modern drugs in line with the intent of the groundbreaking Hatch-Waxman Act of 1984 that established generic drugs as we know them.

Just as Hatch-Waxman allowed for exclusivity extensions to incentivize certain kinds of development of branded drugs, such as demonstrating how they should be used in children (*i.e.,* 6-month pediatric extension), similarly this Contractual

[4] If a payer spends $200M/year on a branded drug but gets a 40% rebate ($80M) in exchange for exclusive formulary status, that payer spends a net $120M on the branded drug. If a biosimilar comes along at a 65% discount, then converting all patients to it would result the drug costing the payer $70M a year, $50M less than they are spending now. That is attractive. But if only 10% of patients switch to the biosimilar, then the payer spends $7M on the biosimilar and $180M on the branded drug (since the rebate would be gone), resulting in greater cost. That is how a rebate without interchangeability protects a brand's monopoly from biosimilars.

Genericization would allow for exclusivity extensions to incentivize companies to continue to upgrade their branded drugs.

The Great American Drug Deal

The biotechnology industry I know thrives on solving healthcare problems. Its efforts to stop COVID are on full display, ingenuity flowing like water through the cracks of a rock, searching out its weaknesses. This same ingenuity is also targeted at thousands of more familiar healthcare problems. Hepatitis C infection can now be readily cured with a short course of pills. The lives of many cystic fibrosis patients have been transformed over the past five years with oral medications. At the pace we are developing new treatments, there is a good chance that a mother giving birth to a girl today will never have to worry about her daughter dying prematurely of breast cancer.

This scientific hustle exists on a foundation of public funding for basic science and some public support for drug development. But it is largely fueled by private capital: the cumulative savings of the world, from billionaires to schoolteachers' pension funds, searching for an attractive return. And it is America's willingness to pay high prices for new drugs during their patented period of market exclusivity that is the draw for all this private capital. The fact that other countries pay less than we do for branded drugs is a function of their willingness to deny breakthrough medicines to their citizens and America's resolve to back innovation even if it has to do so on its own. But America relies on drugs going generic to ensure that our country gets value for its investment. And the fact that branded drug revenues are finite keeps scientists and investors constantly working to develop the next breakthrough. Thanks to the mortgage model brought about by the Hatch-Waxman Act, the biotechnology industry evolved into a community of builders that charge finite mortgages. If generic drug quality remains unreliable and newer drugs remain difficult or impossible to genericize, the biotechnology industry risks regressing into rent extracting landlords.

For a free market to work, it cannot allow monopolies to extract high rents indefinitely. America created the FTC to regulate companies that grew into natural monopolies, in some cases breaking them up. America also passed laws that regulated natural monopolies, such as PURPA in 1978, to make sure Americans are not price gouged by electric companies.

As the medical historian Jeremy Greene points out in *Generic,* his excellent overview of how America's generic drug model was negotiated into existence, while other countries tried to control the price of branded drugs, America kept its drug costs in check by requiring branded drugs to go generic. That has been our model and it has worked to control costs and to incentivize innovation. Without genericization, America would be spending hundreds of billions of dollars more per year on branded drugs. Because of generics, America spends about $271B on branded drugs and only $73B on generics.[5] As long as we ensure that all drugs go generic, through competition or contract, then if we are still spending $271B on branded drugs in 2035, it is because all currently expensive drugs have become inexpensive generics and the biotechnology industry has invented an entirely new set of branded drugs. All of these brands will necessarily have to be better than the generic drug foundation on which they stand. We are builders and what we are building will ensure that our children and grandchildren live healthier lives than we do.

We need a Generic Drug Contract with America to ensure the quality of our generic drugs, to ensure that all drugs go generic and offer America value for its investment, to protect the incentives that drive further biomedical innovation from being throttled by the alternate and far worse measure of price controls on branded drugs, to ensure America's drug supply against global disruption, and to revitalize America's heartland with good jobs.

Of course, it is impossible to talk about drugs without also addressing affordability. As we call for quality generics, we must also call on our society to make appropriately prescribed branded drugs affordable to patients via proper insurance, which means not allowing out-of-pocket costs to exceed what patients can afford. Consider why an insurance plan demands that a physician get prior authorization before prescribing a drug and then, upon deciding the drug is appropriate for the patient and granting the authorization, still requires a high out-of-pocket cost. Is that insurer nudging that patient to disregard her physician's recommendation? That is not in-

[5] *https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1591031020789.*

surance and therein lies America's problem with affordability: it lacks a proper healthcare insurance system. The entire drug industry operates on profit margins in the low teens, which means that a price cut across the board of just 20% would wipe out profits and company valuations (and with them the value of executive stock-based compensation), and yet does absolutely nothing to make a $10,000 drug affordable to a patient that struggles with a $6,000 deductible (which means that even if a drug costs $8,000, the patient would still have to cover the entire deductible).

So the Generic Drug Contract with America is really part of the greater Biotech Social Contract, which requires insurance reform to lower out-of-pocket costs for all Americans and extend insurance to everyone. Amid the COVID crisis, the federal government has already seen the wisdom in covering COVID-related costs for the uninsured, a logical public health measure. Hopefully those temporary patches on the gap-ridden system of American healthcare coverage will be made permanent and expanded to other diseases, because cancer, diabetes, and many other disorders are no less a personal crisis for each patient who suffers from them and their families. Indeed, there are reform bills in Congress that propose caps on out-of-pocket costs and pair those limits with reforms targeting drug manufacturers. This Generic Drug Contract with America embraces the genericization of drugs, ensuring that they are efficiently manufactured at high quality in the US, as the reform necessary for the biopharmaceutical industry to hold up its end of the bargain.

There will be those who oppose the Generic Drug Contract with America. They may have good reasons. However, we should dispatch the ones that are clearly untrue. This is not an assault on free trade; this is a necessary response to unreliable trade. This would not be an unprecedented incursion of government price regulations into pharmaceuticals; the government already contracts with individual companies to make the entire US supply of particular drugs where there could not be a reliable and cost-effective "free market," such as pandemic vaccines and other biodefense countermeasures. California is already exploring the possibility of making all of its own generics. The federal government has contracted with Phlow to make many generic drugs that normally would be sourced from overseas.

I am proposing that we think bigger and, over the course of this next decade, make bold strides to repatriate most if not all of our generic drug supply under contracts. We must ensure that we always can look forward to paying off the mortgage of a drug to take possession of an inexpensive, reliable, public good while innovators move on to the next set of upgrades of our medical armamentarium. And someday those too will go generic.

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Statement of Daniel Fabricant, Ph.D., CEO and President

Introduction

The Natural Products Association (NPA) was founded in 1936 to ensure that Americans have access to safe and affordable natural products, and also to promote and protect the interests of retailers and suppliers of natural nutritional foods and natural products. We are the oldest and largest trade association in our industry. While the industry has existed for many years, it has only recently—since the late 1980s—transformed into a major engine of economic growth, customer satisfaction, and job creation throughout the United States.

When the Dietary Supplement Health and Education Act of 1994 (DSHEA) was passed there were an estimated 4,000 dietary supplement products on the market. Twenty-five years later, there are between 50,000 and 80,000 products on the market. This is in large part because more and more consumers are turning to these products to maintain their health and wellness. But the recent outbreak of COVID–19 also reaffirms the importance of consistency from the Food and Drug Administration when regulating imported finished products.

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) requires that manufacturers and distributors who wish to market dietary supplements that contain "new dietary ingredients" notify the FDA about these ingredients. The notification must include information that is the basis on which the manufacturer or distributor has

concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of use recommended or suggested.

Issue

China is the single largest global supplier of cost-effective raw materials for the nutritional supplement industry, responsible for 60% of the ingredients supplied for finished product manufacturing in the nutritional supplement. Furthermore, in the last several years, thousands of dietary supplements have flooded the American market while the number of New Dietary Ingredients (NDI) submitted to the FDA to establish the safety of new dietary ingredients in supplements has dropped.

The FDA recently received a budget increase of $3 million to modernize its regulatory process for dietary supplements. Despite recent budget increases, FDA has failed to take significant action to protect consumers from adulterated products and from the proliferation of CBD products, which still remain illegal in the U.S. NPA has repeatedly requested action from the FDA on CBD, including establishing a safe level of daily consumption.

By neglecting its enforcement obligations on NDIs and CBD products, the FDA has allowed unsafe and untested dietary supplement products into the country, and potentially unsafe products on store shelves. Adulterated ingredients that have not completed the NDI notification process are entering our country at an alarming rate. This puts American consumers at risk and compliant U.S. supplement makers at a terrible disadvantage.

According to industry estimates, about 90% of dietary supplement products on the market are not required to file an NDI because they have been generally recognized as safe. Meaning, they contain dietary ingredients which have been present in the food supply and are generally recognized as safe. However, that means approximately 4,600 products on the market have not received FDA scrutiny. Furthermore, the Agency has only received 1,100 NDINs, highlighting concerns that these products contain counterfeit ingredients.

When a dietary ingredient is introduced into the food supply for the first time, manufacturers are required to notify the FDA of their intent to market an NDI-containing supplement at least 75 days before the supplement is marketed in the United States. The NDI notification must thoroughly identify the ingredient, how it is used in the supplement, and present evidence the manufacturer relied upon to determine the ingredient is reasonably safe. This provides the FDA with significant oversight on the dietary supplement manufacturers' safety assessment of the NDI-containing dietary supplement.

The Food Safety and Modernization Act (FSMA) directed the Agency to issue guidance pertaining to new dietary ingredients. Specifically, Congress directed the Agency to clarify "when a dietary supplement ingredient is a new dietary ingredient, the manufacturer or distributor of a dietary ingredient or dietary supplement should provide the Secretary with information as described in section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the evidence needed to document the safety of new dietary ingredients and appropriate methods for establishing the identity of a new dietary ingredient."

When an American firm's NDI is acknowledged, its valuable intellectual property is supposed to be protected. However, the Director of FDA's Office of Dietary Supplement Programs admitted that this is not always the case, stating that "it is not all uncommon for stakeholders to say that FDA needs to do a better job of enforcing NDIN. There is a degree of sympathy to that view, but we don't know what we don't know."

Unfortunately, the practice of adulterated products NDIs is all too common, and it harms legitimate manufacturers. Imported dietary supplements are considered adulterated when they purport to contain ingredients that have not gone through the NDIN process or are misrepresenting the ingredients that the dietary supplements actually contain. In 2008, Mitsubishi Gas and Chemical Inc. (MGC) received a successful 2008 NDIN submitted to CFSAN. In 2010, a piggybacked ingredient began to appear on the market before engaging in the FDA's NDIN compliance process for safety concerns. Testing of the product revealed differences between MGC's product and the non-compliant products, including product impurities. When the piggybacked product finally filed NDIs, the FDA questioned the safety of these products, including that the notifier failed to address organ damage after consumption in an experimental animal model. Yet, this product remains on the market. Members of

the Natural Products Association, including, Natural Alternatives International, Lonza, and others all face similar scenarios.

Proposed Solution

NPA proposes a two-pronged public-private partnership approach to ensure the safety of the global dietary supplement supply chain:

Import Alerts: The Agency has not published an import alert for dietary supplements in several years. The agency last used this authority in 2014 in response to safety concerns related to the importation of Kratom. Creating an import alert for new dietary ingredients that have failed to comply with the NDIN regulations would provide the Agency with the ability to police the market in a way that is resource efficient and consistent with the goals of protecting the public's health, and provide the intellectual property protection the industry desperately needs. This process would restore integrity to the NDIN process, protect intellectual property, and provide the necessary safety net our consumers rely on. Since the FDA is prioritizing resources and only performing "for-cause inspections" during the COVID–19 crisis, issuing an import alert for products that are adulterated would require no addition al resources and would be an effective measure that would provide important information to the Agency to facilitate their enforcement of current dietary supplement regulations. Placing responsibility back on the importer to ensure that products being imported to the United States are in compliance with the FDA's laws and regulations is more than an appropriate step providing a necessary safety net for American consumers.

Stronger Self-Regulatory Collaboration: The second recommendation is to expand the number of companies who agree to meet industry specific quality assurance standards in NPA's Supplement Safety and Compliance Initiative (SSCI) SCI is an industry-driven initiative led by the nation's leading retailers to provide a harmonized benchmark to recognize various safety standards throughout the entire dietary supplement supply chain. SSCI is a bold step forward in providing quality assurance from harvest to retailer shelf. Dietary supplements must meet or exceed the SSCI benchmark to be accepted in major retailers, all with the goal of providing quality products and increasing consumer confidence.

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Committee:

It is time to stop implicitly incentivizing the foreign production of drugs. Producing in low-cost countries is cheaper due to lower regulatory costs, not just due to lower input costs. There are ways to lower the incentive to offshore pharmaceutical production:

- Currently, foreign inspections are typically pre-announced; domestic ones are not. Foreign inspections should routinely be unannounced. They must be as stringent as domestic ones.
- Non-domestic producers should be forced to fund the additional costs of running a stringent inspection regime if they want to sell their drugs in the USA. This fee can be location specific. It can partially depend on whether the FDA can rely on a local agency to help regulate production in the chosen production location; it could be waived where regulations and inspection regimes are deemed already comparable (*e.g.,* possibly the MHRA[1] in the U.K.). Blocked visas and

[1] *https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency*.

similar bureaucratic obstructions should be met with the right to refuse import of drugs until inspections are completed.

It is time to make it easier for consumers, doctors, and pharmacists to know not only where their drugs are produced. but to be able to evaluate their quality risk more easily. Unlike many products, it is difficult for consumers, doctors, and pharmacists to detect quality deviations in the drugs they take, prescribe, or administer. In the generics space, which is the vast majority of the market, purchasing and consumption decisions are generally made entirely based on cost.[2] *If quality performance were more transparent, producers of generic drugs can compete on quality, not just cost.*

- Currently, the industry considers the production site of a given drug to be a trade secret. This needs to change. Consumers, doctors, and pharmacists should know exactly where their drugs were made. Specifically, regulations should force transparent "Made In" labeling for drugs, as follows (this can be a website link, QR code, or similar if room on packaging and/or updating packaging is too onerous):
  - Packaged by: (list plant and address)
  - Finished drug product made by: (list plant and address)
  - Active Pharmaceutical Ingredient (API) made in: (list plant and address)
  - Excipients made in: (list countries)

  This, combined with already-available inspection and warning letter information, could make it possible for a consumer, doctor, or pharmacist to get an indication of the quality risk of a drug with reasonable effort. Today, it is extremely difficult to do so, as drugs cannot be linked to their manufacturing plants.
- Beyond providing production location—an important first step—more can be done to make the quality risk of drugs visible. The FDA has been working on risk models[3] for some time, creating risk scores for plants. Similar risk scores can be created at the drug level. Scores recently have been created for valsartan[4]; it's quite possible other drug-level models exist. Once these risk scores are determined to be reasonably predictive of drug problems in the field (the definition of "reasonably" can be made public; *i.e.,* what is the predictive accuracy for what dependent variable?), these risk scores should also be made available.
- Even better, third-party testing of scientifically valid random samples should be performed and made public, at least to healthcare professionals. Valisure[5] has created a market for itself as "the pharmacy that checks." But, why should pharmacies have to test drugs to ensure their safety? CVS and Walgreens do not do this, meaning that the majority of consumers get drugs that rely on testing by the firms selling the drugs. I make two points about the testing of drugs for quality:
  - Unlike many consumer products, consumers/patients generally cannot know if there is a problem with their drug by looking at it. Further, even after taking the drug, it is hard to pinpoint that any side effects are the result of drug quality. This lack of quality visibility makes testing more critical in the drug industry than in many other industries. It also increases the risk that manufacturers, facing cost and delivery pressures, allow drugs to be shipped that did not meet all process and/or product specifications.
  - Relatedly, testing the quality of drugs is not as easy as testing many consumer products. Take, for example, electronics. Electronics production lines often have functionality testing built in, as the last step of the process, meaning that 100% of the product are tested for all—or at least most—potential defects. 100% of drugs cannot be tested, as the tests are destructive. Further, 100% of possible defects cannot be tested. For example, unforeseen contaminants, for which tests are not conducted, could enter the drug supply. Or, processing steps could not be followed in a way that affects stability (*i.e.,* the efficacy and safety of the drug over time); such process deviations may not be evident from tests conducted shortly after production. Further, testing is typically at the batch level. As more production moves to continuous manufacturing, isolating the drugs affected by a test becomes more difficult.

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[2] *https://pubmed.ncbi.nlm.nih.gov/23337525/.*
[3] *https://www.fda.gov/media/116004/download.*
[4] *https://www.medrxiv.org/content/10.1101/2020.05.22.20110775v1.*
[5] *https://www.valisure.com/.*

- Transparency in drug manufacturing location and quality will make it more profitable to operate with high quality, and less profitable to operate with low quality. The market, with knowledge of quality, will be willing to pay more for high-quality drugs and less, or possibly nothing, for low-quality drugs. This will naturally lead to higher levels of quality being built into the manufacturers' processes, through market mechanisms.

It is also time to treat drug availability as a national security issue. Regulators should not be caught between a rock and a hard place in deciding whether to shut down the production of potentially low-quality drugs at a plant and risk a shortage, or whether to allow potentially compromised product into the market to ensure drug availability. Government planning should include:

- Identifying drugs whose shortage could pose a national security threat.
  - Consider Active Pharmaceutical Ingredients (APIs) and even excipients in this analysis (*i.e.,* the upstream components needed to produce these drugs).
- For these drugs, ensure domestic capability exists to produce them; or to ramp up production in the time before shortage (again, including APIs and excipients). Or, increase the availability of these drugs after a supply loss using the stockpile[6] (the stockpile needs to be cycled through regularly to avoid expiration). The investment in capacity to produce/ramp-up vs. investment in the stockpile is a tradeoff that will depend, among other things, on: the shelflife/stability of the drug (and the cost to store), the cost of production capacity, and the time to ramp up new capacity. It needs to be a drug-by-drug analysis.

These regulatory fixes should lead to improvement in both the quality and availability of drugs.

Sincerely,

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The FDA witnesses in the Senate's *COVID–19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process* hearing provided expert testimony on the nuances of regulating medication during the COVID–19 pandemic. The global nature of America's pharmaceutical supply chain inherently complicates FDA efforts to safeguard the American consumer. As a member of the FDA's Emerging Technology Program, TruTag stands ready to assist the FDA and the American public in ensuring that both regulators and consumers have the ability to verify that their medication is manufactured in certified facilities, regardless of packaging.

The stresses on the medical supply chain presented by the COVID–19 pandemic require novel solutions to ensure that criminal entities cannot take advantage of American consumers. Two key points mentioned by the FDA witnesses in the June 2nd Senate hearing are the importance of developing new enforcement and regulatory tools and an emphasis on increasing transparency and accountability in the pharmaceutical supply chain. TruTag Technologies' proprietary silica microtagging is perfectly suited for supporting both of these critical tasks. By encoding existing silica coatings with precise spectral signatures, TruTag Technologies has been able to create a tracking solution which seamlessly meshes with pharmaceutical manufacturing without increasing the cost to consumers. Not only can regulators leverage TruTag Technologies' innovation to verify pharmaceutical origin, facilitating regulatory agility in the event of new public health crises, counterfeiting, or diversion; TruTag Technologies' mobile app enables the American consumer to directly confirm the identity and composition of their medication, regardless of packaging or labeling. Additionally, because TruTags are integrated into the pill coatings themselves, TruTags are impossible to counterfeit, unlike existing serialization and QR code techniques.

We at TruTag Technologies applaud the FDA's efforts to catalyze new technological development to ensure that the United States has access to an extensive supply of verified, safe pharmaceuticals; we urge our legislators to support the FDA in this vital role.

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[6] *https://www.phe.gov/about/sns/Pages/default.aspx.*

It is incontrovertible that the COVID–19 pandemic has exposed vulnerabilities in the medicine supply chain. As outlined in our comments below, USP believes that now is the time to put in place policies and investments to build a more resilient supply chain to help ensure patient trust in the consistent supply of safe, quality medicines and medical products.

We greatly appreciate the Committee's effort to ensure that the medicines Americans rely on meet the quality expectations reflected in federal law. The United States drug supply is among the safest in the world. However, given the complexity of the global supply chain for medicine and the vulnerabilities exposed during this pandemic, we believe that it is imperative to take specific steps to strengthen it. Within this context, we are pleased to submit the following statement for the record on the hearing "COVID–19 and Beyond: Oversight of the FDA's Foreign Manufacturing Inspection Process."

Increase transparency in the global supply chain for medicines

Over the last decade, drug manufacturing in the United States has become increasingly dependent on foreign sources for both finished drug products and active pharmaceutical ingredients (API). It is estimated that 70% of API manufacturers for products intended for the U.S. market are located outside of the United States, mostly in China and India. In this respect, the supply chain is not "global" but is "concentrated," which creates considerable risk when acute disruptions occur and raises concerns about America's ability to ensure the availability of essential medicines. This was evident earlier this year when cities in China shut down and the production of some medicines was halted. India also restricted the export of certain medicines. Disruptions such as geopolitical crises, natural disasters, and pandemics like COVID–19 can cause major interruptions in the supply of quality medicines and have a global impact.

USP believes that more transparency is needed in order to more accurately pinpoint where medicines and their ingredients are produced. For example, while API manufacturers are currently required to register with FDA, they do not have to report the quantity of API they produce. By requiring API manufacturers to report quantities, FDA would have a clearer picture of how much API is produced and by which manufacturers. Furthermore, while there has been a greater focus on API, there are other, inactive ingredients, also known as excipients, that comprise a finished drug product. Additional transparency over the source and quantity of these ingredients is needed.[1] Drug labeling requirements are also essential in tracking the supply chain of medicines.

Invest in advanced manufacturing technologies for domestic production of the most critical medicines and API

Among the key elements necessary to build a more resilient supply chain is the development and adoption of advanced drug manufacturing technologies such as continuous manufacturing. Continuous manufacturing is an approach that automates and integrates medicine production from start to finish. This reduces the capital investment, physical footprint, and environmental impact compared to traditional batch manufacturing. Continuous manufacturing, if broadly adopted, will greatly increase efficiency to produce critical drugs and API, while also ensuring adherence to appropriate quality standards throughout the process. This technology has been deployed for the manufacture of several innovator drug products, but it has yet to be adopted on a wider scale for the most essential (and generally generic) medicines that are often needed in a crisis situation.

USP has been working to address barriers to adoption of continuous manufacturing by providing testing and analytical research needed to ensure quality in this process. Further, USP is taking steps to develop training for the workforce needed to broadly operationalize this technology. Specifically, we are engaging with academic research centers, manufacturers, and regulators to identify and articulate appropriate standards and practices that will make advanced manufacturing, including continuous manufacturing, more accessible and feasible for industry uptake.

We are pleased that there is bipartisan support in Congress for legislation (H.R. 4866, S. 3432) that would help promote development of continuous manufacturing through designation of National Centers of Excellence in Continuous Pharma-

[1] USP's policy paper on building a more resilient supply chain includes additional recommendations for addressing vulnerabilities in the global supply chain (see Attachment 1).

ceutical Manufacturing. As proposed, only qualifying institutions of higher learning would be eligible for designation as a Center of Excellence. We believe that other non-profit organizations, such as USP, could play an important role in this space and urge that the definition of eligible institutions be expanded to include qualifying non-profit organizations. USP supports this legislation and believes that we can play a robust role in helping to accelerate adoption of continuous manufacturing.

Additionally, as Congress considers further action to combat COVID–19 and strengthen the pharmaceutical supply chain, USP urges that additional resources be made available to federal agencies to support advanced manufacturing, and that incentives, including market-based initiatives, are provided to better enable manufacturers to invest in these new technologies.

Invest in a comprehensive Strategic National Stockpile (SNS)

The pandemic has exposed areas for improvement in the breadth of the nation's stockpile of medicines and medical equipment as well as important ancillary products. As the United States re-evaluates the SNS and bolsters its ability to prepare for, and respond to a pandemic, USP believes that ensuring the quality of medicines in the SNS, preparing for the need to test the quality of medicines purchased to respond to a pandemic, and enhancing medicine manufacturing capacity should be priorities.

In response to a request for information from the Department of Health and Human Services, we proposed that USP reference standards be part of a managed initiative that makes these standards[2] readily available to help ensure the quality of drugs and other medical products included in the SNS (see Attachment 2). Enabling readily available access to USP reference standards would:

1. Allow government agencies to evaluate the quality of medicines purchased to respond to public health emergencies, regardless of the manufacturer or manufacturing process;
2. Help the government evaluate and ensure the continued quality of medicines in the SNS; and
3. Help industry and government-funded programs expand manufacturing capacity of medicines associated with public health emergencies, such as the COVID–19 pandemic.

Utilize public standards to identify impurities in drug products

The significant safety concerns associated with unsafe levels of certain impurities in drug products were recently underscored when nitrosamine impurities were found in some widely used medicines, leading to major product recalls.

Insights gained from the toxicological science and sources of impurities, such as nitrosamines, can be applied to develop risk-based approaches to address impurities of potential concern. USP is working to support manufacturers and regulators with tools and solutions for testing, assessing risk, and understanding potential sources of these impurities. For example, we are developing a documentary standard, in the form of a general chapter,[3] that provides broadly applicable risk-based approaches and validated tests for manufacturers, with accompanying physical reference standards that can be used to verify that a medicine and its ingredients pass tests to ensure adherence to quality requirements. These will be available later this summer. We are confident that these tools (which are validated at USP laboratories), will be useful resources to improve product quality. In the longer term, USP is working on

[2] USP public quality standards include two components that work together: documentary standards and reference standards. Documentary standards include monographs, which are substance-specific or product-specific and articulate the quality expectations for a medicine, including its identity, strength, and purity. Documentary standards, both in monographs and in general chapters, also describe the tests to validate that a medicine and its ingredients meet these criteria and provide tests to predict and demonstrate how the medicine will be released as it enters the human body. These standards are included in the United States Pharmacopeia-National Formulary (USP–NF) online platform. A USP physical standard, also known as a reference standard, is a highly characterized specimen of a drug substance or ingredient that facilitates testing to the specifications outlined in the USP–NF. Reference standards are used in conjunction with documentary standards to verify that a medicine and its ingredients adhere to quality requirements. They are rigorously tested and evaluated by multiple independent commercial, regulatory, and academic laboratories to confirm accuracy and reproducibility.

[3] USP general chapters are documentary standards that provide broadly applicable information to industry on accepted processes, tests, and methods to support product development and manufacturing for innovative, generic, and biosimilar medicines.

risk-based predictive tools for handling impurities so that problems can be detected earlier, in the hopes of preventing large-scale drug recalls.

When testing for impurities in general, it is essential to use a method demonstrated to be suitable for its intended purpose. Use of inappropriate tests and methods can increase the risk of generating misleading results, potentially leading to poorer quality of medicines and/or requiring industry and regulators to perform potentially unnecessary follow-up. This can impact the supply chain and has the potential to undermine patient and practitioner confidence in essential medicines.

Advances in chemistry make it possible to synthesize drug components using different methods, which can lead to the development of impurities that were not present in previous manufacturing processes. Impurities included in a USP monograph represent those expected to be present in a product when manufactured under the conditions approved by FDA in a specific drug application. Post-approval changes in synthesis and manufacturing processes can introduce new impurities that monograph tests are not designed to detect. Manufacturers are required to share such process changes and information about new impurities with FDA.

Greater transparency and increased information sharing through the creation of a shared systematic mechanism between industry, FDA, and USP regarding impurities in drugs (including their presence, acceptable limits, and control) can help ensure that standards are updated to include the most current and relevant quality and safety information for all manufacturers. Furthermore, faster detection of impurities can occur if manufacturers and regulators can publicly share information on new impurities, as appropriate.

Conclusion

We thank the Committee for holding this hearing and drawing attention to these important patient safety and medicine quality concerns as we continue to address the impact of COVID–19. USP looks forward to providing information and expertise and is committed to continue working with Congress, FDA, and stakeholders to advance our shared goal of helping to ensure the supply of quality medicines for patients.

About USP

USP is an independent, scientific, non-profit organization dedicated to improving health through the development of public quality standards for medicines, foods, and dietary supplements. Having created quality standards for medicines in and outside of the United States for 200 years, USP has a unique lens into the global medicine supply chain. Today, we provide thousands of manufacturers around the world with critical standards for ensuring the safety and quality of their medicines, including API.

Our mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. USP standards are developed by Expert Committees and Panels comprised of more than 800 independent, scientific experts who collaborate in a transparent process. USP is governed by more than 460 organizations from the scientific, healthcare practitioner, consumer, and industry communities, including dozens of government agencies, who together comprise the USP Convention.[4] Our staff are based in the United States and around the world in locations where America's medicines and their ingredients are manufactured, including India and China. USP staff work with regulators, industry, health care practitioners, and other stakeholders to help ensure that our standards are utilized effectively to safeguard patients.

In addition to being legally recognized in the United States, USP standards are recognized in the laws of 40 other countries and are utilized in more than 150 countries. While there are many components to the regulatory framework to safeguard medicine quality, publicly available quality standards and adherence to them remain foundational.

[4] USP's other governing bodies include its Board of Trustees, Council of Experts, and Expert Committees.

Attachment 1

USP Global Public Policy Position

Key Elements to Building a More Resilient Supply Chain

Issue

Today, patients in the United States and around the world depend on medicines—and the ingredients used to make those medicines—sourced from and manufactured around the globe. This global supply chain for medicines, while providing some inherent risk mitigation, has numerous vulnerabilities that can be challenged by acute disruptions. When such a disruption occurs, concerns arise regarding the quality and safety—as well as shortages—of medicines, particularly those used for critical treatments. Unfortunately, the COVID–19 pandemic brought these impacts into sharp focus.

11 Key Elements for a More Resilient Supply Chain

USP supports a comprehensive public policy framework to build a more resilient supply chain, including advancing the use of pharmacopeial standards across the supply chain, to help ensure the supply of quality medicines. We propose the following key elements be integrated into policy frameworks to build more resilience into the medicines supply chain.

Foster more, not less, supply chain diversity

1. Increase geographic diversity for ingredients and manufacturing—Policymakers should incentivize geographic diversity among the sources of medicine ingredients and drug manufacturing to reduce the risk of shortages from acute disruptions that occur in one geographical location (*e.g.,* earthquake, hurricane, political disruption) or that move from one part of the world to others (*e.g.,* pandemic).
2. Establish baseline of local production capacity—Governments and manufacturers should facilitate the development of local production capabilities to secure a supply of essential quality-assured medicines and vaccines for their population when acute disruptions arise.

Invest in more manufacturing capacity for critical medicines

3. Facilitate an adequate supply of therapeutics and vaccines—Governments should help ensure an appropriate supply of the medicines and vaccines needed to address the most urgent public health concerns by leveraging capital investments to facilitate additional manufacturing capacity, implementing policy reforms to encourage greater competition, and ensuring access to quality and affordable medicines.
4. Invest in advanced technologies—Governments should incentivize advanced technologies (*e.g.,* continuous pharmaceutical manufacturing) through direct investments and other measures to enable more efficient and nimble production of essential medicines and vaccines and to buffer against disruptions in supply during a global crisis.

Enable more transparency and data sharing

5. Increase transparency across the supply chain—To enable appropriate actions—in and across countries—to address and avoid potential supply chain concerns, governments should expand public reporting requirements to healthcare providers and industry for indicators on existing or potential drug shortages. Drug manufacturers and ingredient suppliers should be required to monitor and report to governments on their capacity and the quality of ingredients they source.
6. Enhance global cooperation—Pharmacopeias and regulators around the world should increase information-sharing and consider recognition and reliance agreements. This will help to efficiently mobilize resources during public health emergencies such as pandemics, coordinate access to essential medicines and vaccines, and disincentivize a market for substandard and falsified medicines.

Conduct crisis contingency planning and action

7. Require contingency planning—Policymakers should encourage and incentivize medicine manufacturers to develop backup plans, including for production lines and quality control. Manufacturers of critical medicines also should have other redundancies in place in the event of an acute disruption, to ensure continued access to quality medicines.

8. Build and maintain critical medical product stockpiles—Governments should build and maintain stockpiles of critical medicines and medical products to be prepared to meet the needs of patients and healthcare providers if product shortages result from a crisis. The composition of products in national stockpiles should be continually reviewed and modified to address the most likely shortages of the most critical products. Medical supplies to protect the safety of frontline healthcare workers should be a priority.
9. Plan for distribution resilience—Governments should issue enforceable guidance to ensure the free flow of ingredients and materials (including quality standards and physical reference standards) to enable medicine manufacturing to continue during a crisis. In addition, governments should develop contingency plans to ensure that distribution logistics are in place to transport critical medical products to providers.

Strengthen regulatory systems and quality assurance

10. Strengthen regulatory oversight—Governments should invest in stronger regulatory systems that can efficiently review applications for therapeutics and vaccines, and enforce existing regulations that protect patient safety, including adherence to quality standards. Reliance mechanisms or regional regulatory systems can operate as networks to share information on quality, efficacy, and safety, thereby reinforcing regulatory oversight.
11. Bolster quality assurance systems and adherence to public quality standards—Regulators should strengthen quality assurance systems through investments in workforce training and national drug quality control laboratories and should stress adherence to science-based public quality standards, which are essential to maintaining the trust of healthcare professionals and patients in medicine quality. Moreover, countries around the world should ensure compliance to international standards, including good manufacturing practices and science-based public quality standards, so that medicines and ingredients from more locations can be trusted in the global supply chain.

Discussion

Over the last decade or so, global medicines supply chains have moved from being vertically integrated, where a drug manufacturer owns or controls most aspects of production (including suppliers), to horizontal, where many functions in the supply chain (such as the production of both active pharmaceutical ingredients (APIs) and inactive ingredients) are increasingly outsourced to many companies around the world. In many cases, these companies are concentrated in certain geographical areas.

The COVID–19 pandemic has exposed vulnerabilities in the current way the medicines supply chain works, including geographically concentrated sourcing and manufacturing, uneven regulatory environments, and regulatory enforcement or inspection capacity constraints. Many countries may soon, if they have not already, face disruptions such as medicine shortages, concerns over substandard or falsified medicines, and price volatility. Having policies in place to build a more resilient supply chain can help ensure the continued availability of safe, quality medicines for patients around the globe-even in times of a pandemic crisis. While the current COVID–19 crisis points to the supply chain impact of a pandemic, other acute supply chain disruptors include weather events such as hurricanes and earthquakes, as well as product recalls.

The globalization of supply chains has led to geographic concentration of manufacturers of both ingredients and finished medicines in certain locations where labor and raw material costs may be lower, environmental regulations more permissive, and infrastructure subsidized by the public sector. While this concentration has likely led to lower costs for many medicines and their ingredients, it poses a risk to the reliability of supply in crisis situations and raises quality and safety concerns.

During a pandemic, sourcing from only a few countries can have unintended consequences. For example, countries that make medicines and APIs may withhold essential public health resources—including therapeutics intended for COVID–19—as well as other therapies needed to address national health priorities. For instance, India briefly withheld exports on selected medicines, including some antibiotics and painkillers, and has restricted the export of antimalarials now being considered as

potential (though still unproven) treatment options for COVID–19.[1, 2] Countries may also compete with each other to procure medications. Diversifying sources of both pharmaceutical ingredients and finished medicines can help reduce the risk of concentration in only one place, and appropriate incentives to facilitate this diversification should be considered.

Increased line-of-sight across all parts of the supply chain can also help make the supply chain stronger. Regulators, along with pharmacies, hospitals, and providers, need to know more about where medicines and ingredients are manufactured and how they have passed through the supply chain. This information can inform risk mitigation decisions and help governments and providers plan for the supply of quality medicines needed to treat patients. This is essential to building and maintaining the public's trust.

Today, regulators have limited and inconsistent information on the sources of the ingredients in medicines or the volume of medicines produced from manufacturing facilities around the world. Information-sharing between regulators and industry is also needed to see clearly across the supply chain. New reporting requirements for finished drug products and ingredient makers can increase transparency and should be balanced with appropriate protections for trade secrets and confidential commercial information. Further, if manufacturers can use new technologies (*e.g.,* AI) to strengthen their ability to monitor their suppliers, and thereby understand the global presence of both their suppliers and their subcontractors, they may be able to mitigate problems more immediately as they arise.

A requirement for drug and API manufacturers to develop contingency plans in the event of a disruption in production would help to ensure a continued supply of quality medicines. Such measures should include establishing alternative sources of API and other ingredients, shifting production lines, and implementing quality control. These contingencies should also apply to ensuring the availability of medical products such as personal protective equipment, bags for intravenous fluids, syringes, and other supplies needed to provide care that would be impacted by supply chain disruptors.

Strong regulatory oversight is needed to withstand disruptions in the supply chain. Strengthened oversight by regulatory authorities includes deployment of tools such as supplier verification and audits to ensure the quality of ingredients, along with track-and-trace mechanisms to determine drug and ingredient current and past locations. Risk-based analysis can help countries understand the most critical—or vulnerable—points in the supply chain. In the absence of tracking and tracing of products, especially as the supply chain diversifies, quality testing can serve as a last line of defense. During times of crisis, aggressive enforcement action by regulatory bodies against substandard and falsified products, unverified or false claims of treatments or cures, and price gouging, is needed to prevent further harm.

Advanced manufacturing technologies, such as continuous manufacturing, provide more streamlined, consistent, and efficient production of medicines than traditional approaches. Efforts to operationalize this technology, including incentives to allow for its rapid deployment, should be pursued. Given the current global pandemic, countries should incentivize and accelerate longer-term efforts to help expand the continuous manufacturing infrastructure in both the United States and in other countries for generic and branded medicine production.

Enhanced global cooperation can help countries secure critical medicines, especially in light of challenges caused by border closures as a result of COVID–19. Regulatory authorities that share information have expedited the approval of essential vaccines and medicines, prevented the distribution of substandard and falsified medicines, and quickly mobilized resources during drug shortages and public health emergencies. A recognition or reliance arrangement, whereby one agency recognizes or relies on another's work as equivalent to its own, allows medicine regulators to make use of shared information while being able to make their own decisions. Examples of information that regulators can share with each other include clinical assessments, manufacturing site inspections, and post-market safety data.

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[1] Government of India Ministry of Commerce and Industry. Department of Commerce. Directorate General of Foreign Trade. Amendment in Export Policy of APIs and formulations made from these APIs. New Delhi. March 3, 2020. *https://dgft.gov.in/sites/default/files/Noti%2050_pdf.*

[2] Government of India Ministry of Commerce and Industry. Department of Commerce. Directorate General of Foreign Trade. New Delhi. Amendment in Export Policy of Hydroxychloroquine. *https://dgft.gov.in/sites/default/files/notification%2054_0.pdf.*

Maintaining the quality of medicines during a global crisis is paramount to ensuring they work in the way they are intended. In responding to disruptions, countries may purchase medicines from untested suppliers, which in turn could create a market for substandard or falsified medicines.[3] Low- and middle-income countries are especially vulnerable, as their already under-resourced regulatory systems would come under additional stress. Consumers may also buy medicines from the Internet, where oversight is weaker and bad actors proliferate. In addition, the urgency to develop new therapeutics and vaccines cannot be separated from the need to assure quality. Ensuring pharmacopeial standards are met across the supply chain can help regulators and industry ensure continued access to quality medicines.

Encouraging greater competition, especially for products with either a single source or few manufacturers, would help lead to increased access to critical medicines. Once a vaccine for COVID–19 is discovered and approved for use, local capacity to manufacture may become a priority to ensure widespread, equitable, and rapid distribution.

It also is important that governments plan for resilience in distribution. Regulators should issue standing guidance that clarifies the ingredients, materials, and standards that must remain available in global commerce for the manufacture of critical medicines. Moreover, contingencies for the transport of medicines and medical supplies is essential to account for the potential malfunction of traditional transportation modalities in a crisis situation. In addition to contingency planning for medicines, it is equally essential for personal protective equipment to protect the safety of frontline healthcare workers. Distributors, including wholesalers, must follow good distribution practices to assure medicine and ingredient quality through procurement, purchasing, transport, distribution, repackaging, relabeling, storage, and documentation. Logistics and transport considerations are critical to ensuring essential medicines can make it to patients.

Finally, to be prepared to meet the needs of patients and healthcare providers if product shortages result from a crisis, governments should build and maintain stockpiles of critical medicines and medical products with unexpired inventory. The composition of products in national stockpiles should be continually reviewed and modified to address potential shortages of the most critical medical products.

Call to Action

USP encourages investment and policy reform toward building a more resilient global supply chain. The current vulnerabilities in the supply chain are the result of a number of factors, so solutions to address these vulnerabilities must account for these variations. The key elements outlined above require action by all those in the supply chain, including manufacturers, distributors, policymakers and regulators, and public health experts.

About USP

Founded in 1820, USP is an independent, nonprofit, science based organization that safeguards the public's health globally by developing quality standards for medicines, dietary supplements, food ingredients, and healthcare quality. USP standards describe specifications and tests for identity, strength, quality, and purity. USP standards are enforceable by the U.S. Food and Drug Administration (FDA) for medicines and their ingredients imported into or marketed in the United States and have been used in more than 140 countries. Such standards also assist industry in the development, manufacturing, and testing of medicines. USP standards are developed by independent experts through a transparent scientific process, with input from stakeholders and federal agencies such as FDA and the Centers for Disease Control and Prevention.

USP's Promoting the Quality of Medicines Plus (PQM+) program improves access to quality-assured priority medicines and addresses the proliferation of poor-quality medical products in low- and middle-income countries. PQM+ strengthens medical product quality assurance systems in low- and middle-income countries through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system.

USP is implementing a comprehensive program to support the public health response to the COVID–19 pandemic. Our immediate work is focused on facilitating the supply of quality medicines across the global supply chain—especially for those

[3] Pisai, Elizabeth. "The COVID pandemic increases the chance that your other medicines won't work." *Medium.* March 29, 2020. *https://medium.com/@elizabethpisani/the-cov1d-pandemic-increases-the-chance-that-your-other-medicines-wont-work-66b7e272bb20.*

medicines that treat symptoms associated with the virus—by working closely with regulators, manufacturers, and other stakeholders around the world. We are also engaging in middle- and long-term activities to assess vulnerabilities in the global supply chain for medicines, advocate for greater transparency and more diversity in the sources of medicines and their ingredients, and ultimately help build a more resilient supply chain.

Atttachment 2

June 3, 2020

U.S. Department of Health and Human Services (HHS)
Office of the Assistant Secretary for Preparedness and Response (ASPR)
Division of the Strategic National Stockpile (DSNS)

Re: RFI # 75A50120NEXTGENSNS

Dear Sir/Madam,

The United States Pharmacopeia (USP) appreciates the opportunity to provide comments in response to the request for information (RFI) from HHS/ASPR/DSNS on the Strategic National Stockpile (SNS). USP is an independent, scientific, nonprofit public health organization founded in 1820 that works to improve health through the development of public standard s and related programs that help ensure the quality, safety, and benefit of medicines and foods.

USP's public standards define quality expectations for medicines and are developed by Expert Committees and Panels, which are comprised of over 1,000 independent, scientific experts and include the participation of over 100 government liaisons from the Food and Drug Administration (FDA). The *United States Pharmacopeia-National Formulary (USP–NF)* includes over 5,000 documentary quality standard s for drug substances and drug products.[1] Material reference standards are used in conjunction with these documentary standards to verify that a medicine and its ingredients can pass tests to ensure adherence to quality requirements. USP standards are legally recognized in the United States and are used in more than 150 countries.

Response to Section 1/Question 1—"Do you agree with the stated objectives of the SNS? Have we missed anything major in articulating our vision?"

USP supports the objectives of the SNS and the expansion of public-private partnerships. USP believes that a contempora1y SNS will need to include an appropriate volume of the most critical medicines, manufactured and maintained to quality expectations. To ensure the quality of these medicines, as well as any that are manufactured and purchased by the U.S. government during a crisis, the SNS should also include the USP material reference standards required to test these medicines.

As explained in more detail below, enabling readily available access to USP reference standards would: (1) help industry and government-funded programs expand manufacturing capacity of medicines associated with pandemics, such as COVID–19; (2) allow government agencies to evaluate the quality of medicines purchased to respond to a pandemic, regardless of the manufacturer or manufacturing process; and (3) help the government evaluate and ensure the continued quality of medicines in the SNS.

Response to Section 1/Question 3—"How can your organization contribute to achieving the vision for the SNS?"

USP stands ready to help ensure that the medicines in the SNS are quality assured. Specifically, we propose that USP reference standards be part of a managed initiative that makes reference standards for stockpiled medicines available to test medicines in the SNS for their quality.[2] Readily available standards will enable regulators to evaluate and ensure the quality of medicines in the SNS. Moreover, a managed SNS invento1yof reference standards would support industry and government-funded programs to expand the manufacturing capacity for quality medicines during

[1] USP standards are developed through an open, transparent, expert-based process, offering the ability to respond to public health emergencies, adapt to new industry practices, and support evolving science and technology.

[2] USP also recommends including in the SNS items such as chromatography equipment and substances (*e.g.,* reagents) for use in conducting tests and analyses with reference standards.

a crisis. It is essential for public health and patient safety that the quality of drugs in the SNS is ensured, and reference standards are necessary to do this.

As stated above, USP public quality standards include two components that work together: documenta1y standards and reference standards. **Documentary standards** are substance-specific or product-specific that articulate the quality expectations for a medicine, including its identity, strength, and purity. Documentary standards also describe the tests to validate that a medicine and its ingredients meet these criteria. These are included in the *USP–NF* online platform in the form of monographs. A USP physical standard, also known as a **reference standard,** is a highly characterized specimen of a drug substance or ingredient that facilitates testing to the specifications outlined in the *USP–NF.* Reference standards are used in conjunction with documentary standards to verify that a medicine and its ingredients adhere to quality requirements.[3] They are rigorously tested and evaluated by multiple independent commercial, regulatory, and academic laboratories to confirm accuracy and reproducibility.

In addition to being required for quality testing, reference standards and access thereto in a time of crisis facilitate the expeditious production of quality medicines for the SNS. USP reference standards support manufacturer's ability to test its products during the drug manufacturing process. Ready access to standards—both documentary and reference—is especially needed, and in greater quantities, when drug manufacturing is increased to meet a surge in demand.

In response to increased demand for pa1iicular drug products related to the current pandemic, USP has taken steps to ensure continued operations of essential services, including the production of reference standards, to minimize disruptions and support the medicines supply chain. Looking ahead, however, it is difficult to predict all rapid increases in demand. Setting aside specific reference standards maintained at USP facilities in Ma1yland to support the SNS will help secure capacity and support production of critical medicines, particularly in a time of crisis. USP can work with HHS/ASPR/DSNS to determine which reference standards, and the volume of each standard, are needed for the current and evolving stockpile.

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Thank you again for the oppo1iunity to comment on this RFI. USP stands ready to work with HHS/ASPR/DSNS to help support manufacturer capacity to produce drugs that meet quality standards. For more information, please contact Carrie Harney, Senior Director, Government Affairs, Policy and Advocacy, at cxh@usp.org or (202) 239–4136.

Sincerely yours,

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[3] Additional information on the use of reference standards can be found in guidances from the Food and Drug Administration (FDA) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). *See* "Analytical Procedures and Methods Validation for Drugs and Biologics," at *https://www.fda.gov/files/drugs/published/Analytical-Procedures-and-Methods-Validation-for-Drugs-and-Biologics.pdf;* "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products," at *https://www.fda.gov/media/71510/download;* and "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," at *https://www.fda.gov/media/71518/download.*