SECURING THE U.S. DRUG SUPPLY CHAIN: OVERSIGHT OF FDA'S FOREIGN INSPECTION PROGRAM

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTEENTH CONGRESS

FIRST SESSION

DECEMBER 10, 2019

Serial No. 116–83

Printed for the use of the Committee on Energy and Commerce

govinfo.gov/committee/house-energy
energycommerce.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE

44–495 PDF WASHINGTON : 2021

COMMITTEE ON ENERGY AND COMMERCE

FRANK PALLONE, JR., New Jersey
Chairman

BOBBY L. RUSH, Illinois
ANNA G. ESHOO, California
ELIOT L. ENGEL, New York
DIANA DEGETTE, Colorado
MIKE DOYLE, Pennsylvania
JAN SCHAKOWSKY, Illinois
G. K. BUTTERFIELD, North Carolina
DORIS O. MATSUI, California
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
JERRY MCNERNEY, California
PETER WELCH, Vermont
BEN RAY LUJAN, New Mexico
PAUL TONKO, New York
YVETTE D. CLARKE, New York, *Vice Chair*
DAVID LOEBSACK, Iowa
KURT SCHRADER, Oregon
JOSEPH P. KENNEDY III, Massachusetts
TONY CÁRDENAS, California
RAUL RUIZ, California
SCOTT H. PETERS, California
DEBBIE DINGELL, Michigan
MARC A. VEASEY, Texas
ANN M. KUSTER, New Hampshire
ROBIN L. KELLY, Illinois
NANETTE DIAZ BARRAGÁN, California
A. DONALD MCEACHIN, Virginia
LISA BLUNT ROCHESTER, Delaware
DARREN SOTO, Florida
TOM O'HALLERAN, Arizona

GREG WALDEN, Oregon
Ranking Member
FRED UPTON, Michigan
JOHN SHIMKUS, Illinois
MICHAEL C. BURGESS, Texas
STEVE SCALISE, Louisiana
ROBERT E. LATTA, Ohio
CATHY MCMORRIS RODGERS, Washington
BRETT GUTHRIE, Kentucky
PETE OLSON, Texas
DAVID B. MCKINLEY, West Virginia
ADAM KINZINGER, Illinois
H. MORGAN GRIFFITH, Virginia
GUS M. BILIRAKIS, Florida
BILL JOHNSON, Ohio
BILLY LONG, Missouri
LARRY BUCSHON, Indiana
BILL FLORES, Texas
SUSAN W. BROOKS, Indiana
MARKWAYNE MULLIN, Oklahoma
RICHARD HUDSON, North Carolina
TIM WALBERG, Michigan
EARL L. "BUDDY" CARTER, Georgia
JEFF DUNCAN, South Carolina
GREG GIANFORTE, Montana

PROFESSIONAL STAFF

JEFFREY C. CARROLL, *Staff Director*
TIFFANY GUARASCIO, *Deputy Staff Director*
MIKE BLOOMQUIST, *Minority Staff Director*

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

DIANA DEGETTE, Colorado
Chair

JAN SCHAKOWSKY, Illinois
JOSEPH P. KENNEDY III, Massachusetts, *Vice Chair*
RAUL RUIZ, California
ANN M. KUSTER, New Hampshire
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
PAUL TONKO, New York
YVETTE D. CLARKE, New York
SCOTT H. PETERS, California
FRANK PALLONE, JR., New Jersey *(ex officio)*

BRETT GUTHRIE, Kentucky
Ranking Member
MICHAEL C. BURGESS, Texas
DAVID B. MCKINLEY, West Virginia
H. MORGAN GRIFFITH, Virginia
SUSAN W. BROOKS, Indiana
MARKWAYNE MULLIN, Oklahoma
JEFF DUNCAN, South Carolina
GREG WALDEN, Oregon *(ex officio)*

C O N T E N T S

SECURING THE U.S. DRUG SUPPLY CHAIN: OVERSIGHT OF FDA'S FOREIGN INSPECTION PROGRAM

TUESDAY, DECEMBER 10, 2019

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:04 a.m., in the John D. Dingell Room 2123, Rayburn House Office Building, Hon. Diana DeGette (chair of the subcommittee) presiding.

Members present: Representatives DeGette, Schakowsky, Kennedy, Ruiz, Kuster, Castor, Tonko, Clarke, Pallone (ex officio), Guthrie (subcommittee ranking member), McKinley, Griffith, Brooks, Mullin, and Walden (ex officio).

Staff present: Kevin Barstow, Chief Oversight Counsel; Jeffrey C. Carroll, Staff Director; Manmeet Dhindsa, Counsel; Austin Flack, Staff Assistant; Tiffany Guarascio, Deputy Staff Director; Chris Knauer, Oversight Staff Director; Kevin McAloon, Professional Staff Member; Kaitlyn Peel, Digital Director; Tim Robinson, Chief Counsel; Nikki Roy, Policy Coordinator; Emily Ryan, GAO Detailee; Andrew Souvall, Director of Communications, Outreach, and Member Services; Benjamin Tabor, Policy Analyst; C.J. Young, Press Secretary; Jen Barblan, Minority Chief Counsel, Oversight and Investigations; Diane Cutler, Minority Detailee, Oversight and Investigations; Peter Kielty, Minority General Counsel; Ryan Long, Minority Deputy Staff Director; Brannon Rains, Minority Legislative Clerk; Kristin Seum, Minority Counsel, Health; and Alan Slobodin, Minority Chief Investigative Counsel, Oversight and Investigations.

Ms. DEGETTE. The Subcommittee on Oversight and Investigations will now come to order.

Today, the subcommittee is holding a hearing entitled, "Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program." The purpose of the hearing is to examine the Food and Drug Administration's ability to effectively oversee the quality of drug products manufactured in foreign countries.

The Chair now recognizes herself for purposes of an opening statement.

OPENING STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Today's hearing focuses on an area of longstanding concern to this committee that has taken on increased importance: The safety and effectiveness of pharmaceutical products made in foreign countries. Between 70 and 80 percent of active pharmaceutical ingredients and 40 percent of finished drugs are made outside the United States. In particular, China and India produce a significant portion of the U.S. drug supply.

Because the FDA can't possibly test every new drug that comes into the U.S., inspections of drug manufacturers abroad are a critical way to ensure that manufacturers around the world are following quality standards and producing drugs that are safe and effective for the American public. However, the history of the FDA's foreign drug inspection program is one of challenges and incremental progress. As far back as 1998, the GAO has been raising concerns with the FDA's foreign inspections.

This committee has a long history of oversight in this area. For example, in 2007, we held a hearing about weaknesses in the FDA's foreign inspections program. At that time, the agency was not conducting frequent inspections abroad and did not have reliable data even to know how many firms it needed to inspect.

FDA also struggled to hire inspectional staff, and its inspectors did not have reliable translators to help them conduct inspections in foreign-language countries. I remember that hearing because I was there, and it was shocking.

The year after that hearing, the world was reminded why securing the global pharmaceutical supply chain is critical, when it was discovered that tainted ingredients were used to produce heparin, which is a critical drug used in surgery and during dialysis. As a result of that mishap, Americans died, drug shortages occurred, and many lost confidence in FDA's ability to regulate drugs manufactured abroad.

GAO's reports over the years have also noted vulnerabilities in how FDA regulates foreign drug manufacturing. For example, in 2010, GAO found that FDA may never have inspected most foreign firms. FDA was also struggling to staff up its foreign offices, which were intended to make foreign inspections more efficient and effective. Because of these and other issues, GAO placed FDA's foreign inspections program on its high-risk list over 10 years ago.

Now, in response to these challenges, Congress increased FDA's resources to conduct foreign inspections and granted the agency new authorities over foreign firms. As a result, the number of inspections FDA conducted increased overseas, and the FDA implemented a risk-based approach to select firms for inspection, regardless of whether they were domestic or foreign.

Now, these were significant improvements, but here we are back today because FDA's foreign inspection program still has some unresolved challenges. In the GAO's written testimony today, there are reports on the results of its recent travel overseas to evaluate FDA's work. GAO still found some of the same issues, unfortunately, that have been hindering FDA's foreign inspection program for years.

The number of foreign inspections dropped in the last 2 years, after years of increases. Furthermore, when FDA conducts inspections in foreign-language-speaking countries, it still relies on the firm itself to provide a translator, raising questions about impartiality. And despite the new resources, FDA continues to struggle to hire enough inspectors, including in the foreign offices, and frankly, there are some real barriers to being able to do that.

These challenges take on real meaning when we see reports of potentially unsafe products in the market. Over the last year and a half, FDA has been announcing widespread recalls of popular medications used by millions of Americans to treat blood pressure and heartburn because of trace amounts of carcinogens identified in multiple versions of these drugs.

Now, I understand each of these recalls involves its own particular causes and factors, but taken together they raise larger issues, and I'm really—Dr. Woodcock, I'm very happy you're here today, because I look forward to hearing what the agency's response is to these new GAO findings.

Before I close, I just want to emphasize a couple final thoughts. First, the issues today affect both brand and generic drugs. Many foreign firms provide the active pharmaceutical ingredients used in both brand and generic versions of drugs, so this can happen throughout the supply chain.

And finally, I want to emphasize, this hearing should not be interpreted as an indictment of foreign drug manufacturing generally. Americans should not feel that they cannot trust medicines made abroad, nor should we swear off foreign-made drugs. In fact, we're increasingly reliant on foreign manufacturers, but we do need to make sure that all of these issues which have been persistent for many, many years continue to be addressed.

And with that, I want to thank both of our witnesses for appearing today.

[The prepared statement of Ms. DeGette follows:]

PREPARED STATEMENT OF HON. DIANA DEGETTE

Today's hearing focuses on an area of longstanding concern to the committee that has taken on increased importance: the safety and effectiveness of pharmaceutical products made in foreign countries.

Between 70 and 80 percent of active pharmaceutical ingredients ("API") and 40 percent of finished drugs are made outside the United States. In particular, China and India produce a significant portion of the U.S. drug supply.

Because the Food and Drug Administration (FDA) cannot possibly test every drug that comes into the U.S., FDA inspections of drug manufacturers abroad are a critical way to ensure that manufacturers around the world are following quality standards and producing drugs that are safe and effective for the American public.

However, the history of FDA's foreign drug inspection program is one of challenges and incremental progress. As far back as 1998, the Government Accountability Office (GAO) has been raising concerns with FDA's foreign inspections.

This committee has a long history of oversight in this area. For instance, in 2007, we held a hearing about weaknesses in FDA's foreign inspections program. At that time, FDA was not conducting frequent inspections abroad, and did not have reliable data to even know how many firms it needed to inspect. FDA also struggled to hire inspectional staff, and its inspectors did not have reliable translators to help them conduct inspections in foreign-language countries.

The year after that hearing, the world was reminded why securing the global pharmaceutical supply chain is critical, when it was discovered that tainted ingredients were used to produce heparin—a critical drug used in surgery and during dialysis.

As a result of that mishap, Americans died, drug shortages occurred, and many lost confidence in FDA's ability to regulate drugs manufactured abroad.

GAO's reports over the years have also noted vulnerabilities in how FDA regulates foreign drug manufacturing. For example, in 2010, GAO found that FDA may have never inspected most foreign firms. FDA was also struggling to staff up its foreign offices, which were intended to make foreign inspections more efficient and effective.

Because of these and other issues, GAO placed FDA's foreign inspections program on its High Risk list over 10 years ago.

In response to these challenges, Congress increased FDA's resources to conduct foreign inspections and granted FDA new authorities over foreign firms. As a result, FDA increased the number of inspections it conducted, and implemented a risk-based approach to select firms for inspection, regardless of whether they were foreign or domestic.

These were significant improvements. But despite that progress, we are back here today because FDA's foreign drug inspection program still has unresolved challenges. In its written testimony today, GAO reports on the results of its recent travel overseas to evaluate FDA's work. GAO found some of the same issues that have been hindering FDA's foreign inspection program for years.

GAO reports that the number of foreign inspections dropped in the last two years, after years of increases. Furthermore, when FDA conducts inspections in foreign language-speaking countries, it still largely relies on the firm itself to provide a translator, raising concerns about impartiality. And despite getting new resources, FDA continues to struggle to hire enough inspectors, including in its foreign offices.

These challenges take on real meaning when we see reports of potentially unsafe products in the market. Over the past year and a half, FDA has been announcing widespread recalls of popular medications used by millions of Americans to treat blood pressure and heartburn, because of trace amounts of carcinogens identified in multiple versions of these drugs.

While I understand each of these recalls involves its own particular causes and factors, taken together, they raise larger issues and concerns that FDA has not fully addressed longstanding vulnerabilities in its foreign inspections program.

Before I close, I would like to emphasize a couple final thoughts. First, the issues we will be discussing today affect both brand and generic drugs. Many foreign firms provide the active pharmaceutical ingredients used in both brand and generic versions of drugs, so these issues can affect drugs throughout the supply chain—which is all the more reason why they must be addressed.

Finally, this hearing should not be interpreted as an indictment of foreign drug manufacturing generally. Americans should not feel that they cannot trust medicines made abroad, nor should we swear off foreign-made drugs. In fact, we are increasingly reliant on foreign manufacturers.

But if drugs are going to be made abroad, then Americans must have confidence in the ability of FDA to effectively regulate foreign suppliers. It is critical that FDA have the resources and the capability to do this job and ensure that every American can trust the safety and effectiveness of the drugs they take.

Ms. DEGETTE. And I'm going to yield to the ranking member of the full Energy and Commerce Committee, Mr. Walden, for purposes of his opening statement, 5 minutes.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Thank you very much, Madam Chair. And I want to thank Ranking Member Guthrie for yielding to me. We've got another hearing I have to get at that conflicts with this one, so—and I want to thank our witnesses for being here. And, Madam Chair, thank you for holding this really important hearing, because our drugs and drug ingredients more and more are coming from overseas, especially from China and India, and manufacturers have ultimate responsibility for the safety and effectiveness of these products.

But the FDA has an indispensable role to protect public health, which I know you all take very seriously, by ensuring that drug

firms are complying with good manufacturing processes and practices. Through this hearing, I hope FDA can further strengthen its ability to fulfill its public health mission and to protect the safety, effectiveness, and integrity of the U.S. drug supply.

Today, we have the benefit of the Government Accountability Office, their analysis, to assist us in our work. Over the years, GAO has provided invaluable work to this committee on FDA's foreign drug inspection program, and not long ago the GAO reported that the FDA was not conducting enough drug inspections overseas and lacked the resources and authorities to adequately meet this inspection need. This committee responded by enacting the Food and Drug Administration Safety Innovation Act or—we'll just leave it at that—and the Generic User Fee Act, or GDUFA—they have all these UFAs and ASIAs and DASIAs and—well, anyway, FDA now has additional resources and authorities and, to FDA's credit, has addressed the previous disparity between the number of domestic and foreign inspections conducted.

Earlier this year, as you know, the committee again asked the GAO, on a bipartisan basis, to evaluate the current state of the foreign drug inspection program. While progress has been made in some areas, the GAO's preliminary observations indicate the FDA continues to face persistent challenges in its ability to conduct foreign drug inspections, and particularly in India and China. This is concerning because the FDA is identifying serious deficiencies during many foreign inspections.

Now, for years, the FDA leadership has spoken of transforming the agency into a global health organization, particularly in addressing imported drugs. But even with that stated priority and the influx of user fees, FDA has told the GAO and this committee that it can't hire enough inspectors to fill vacancies among staff conducting foreign inspections. Now, having sufficient numbers of inspectors is not a new problem. The need to hire additional inspectors was part of the reason that Congress gave the FDA the authority to collect user fees for generic drugs.

Today, FDA not only has vacancies in its foreign offices but also does not have enough inspectors in its dedicated foreign drug cadre. The FDA recently received direct-hire authority to address this problem, and I have questions today about how this authority will be used to fill these vacancies, as well as about FDA's hiring and retention efforts the past 6 years.

Other challenges to FDA's foreign drug inspection program remain, and unlike domestic drug inspections, most foreign drug firms actually receive advance notice of an FDA inspection. And when the FDA inspectors are traveling from the United States, which is often the case in most foreign drug inspections, the FDA preannounces inspections and foreign drug firms generally get 12 weeks in advance with a notice on when the FDA inspectors are coming to their plants. The concerns raised by recent investigative reports is this system gives plants ample time to clean up evidence of unsanitary conditions, wrongdoing, or data manipulation.

And I would just say as a side note, having been a licensee of the FCC for 21 years in the radio business, I always would have liked to have had a 12-week notice in advance when the FCC was

coming to inspect our station. We never got a fine, but we would have made sure everything was completely in order. It always was.

In 2014, to address these issues, the FDA instituted an initiative in India, giving plants only short or no advance notice of inspections, and as a result, the serious violations uncovered by inspectors rose by almost 60 percent. So the initiative was discontinued in 2015. FDA told the committee they discontinued the initiative because it lacked protocols and evaluation criteria.

However, the FDA still must believe there's value to short-notice inspections, because you do conduct such inspections in for-cause situations and conduct short-notice inspections domestically.

Finally, in about 80 percent of the inspections, FDA sends only one inspector, who is often reliant on the drug firm's employees or agents to do the translation. What could go wrong there? This solitary inspector, relying on the firm for translation and perhaps even travel arrangements, is allocated only a few days for the difficult task of inspecting a drug plant that can be the size of a small city.

Meanwhile, the drug firm has about 3 months' advance notice of the inspection. If the firm's unscrupulous, that's more than enough time to subvert regulations by fabricating records and concealing actual conditions. I think you get the point. So FDA needs to respond to the overall challenges of foreign drug inspections with more vigor. As they said in "Jaws," "You're going to need a bigger boat." So we must maintain public confidence and trust in our drug supply chain, and we look forward to working with you to make that happen.

Madam Chair, thank you for having this hearing.

[The prepared statement of Mr. Walden follows:]

PREPARED STATEMENT OF HON. GREG WALDEN

Chair DeGette, thank you for this hearing. Our drugs and drug ingredients more and more come from overseas, especially from China and India. Manufacturers have ultimate responsibility for the safety and effectiveness of these products. But FDA has an indispensable role to protect public health by ensuring that drug firms are complying with good manufacturing practices. Through this hearing, I hope FDA can further strengthen its ability to fulfill its public health mission, and to protect the safety, effectiveness, and integrity of the U.S. drug supply.

Today, we have the benefit of the Government Accountability Office's (GAO) analysis to assist us. Over the years, GAO has provided invaluable work to this Committee on FDA's foreign drug inspection program. Not that long ago, GAO reported that FDA was not conducting enough drug inspections overseas and lacked resources and authorities to adequately meet this inspection need. This committee responded by enacting the Food and Drug Administration Safety and Innovation Act, or FDASIA, and the Generic Drug User Fee Act, or GDUFA. FDA now has additional resources and authorities and, to the FDA's credit, has addressed the previous disparity between the number of domestic and foreign inspections conducted.

Earlier this year, the committee again asked GAO on a bipartisan basis to evaluate the current state of the foreign drug inspection program. While progress has been made in some areas, the GAO's preliminary observations indicate that FDA continues to face persistent challenges in its ability to conduct foreign drug inspections, particularly in India and China. This is concerning because FDA is identifying serious deficiencies during many foreign inspections.

For years, FDA leadership has spoken of transforming the agency into a global health organization, particularly in addressing imported drugs. But even with that stated priority and the influx of user fees, FDA has told the GAO and this committee that it can't hire enough inspectors to fill vacancies among staff conducting foreign inspections. Having sufficient numbers of inspectors is not a new problem—the need to hire additional inspectors was part of the reason that Congress gave FDA the authority to collect user fees for generic drugs. Today, FDA not only has

vacancies in its foreign offices but also does not have enough inspectors in its dedicated foreign drug cadre. FDA recently received direct-hire authority to address this problem, and I have questions today about how this authority will be used to fill these vacancies, as well as about FDA's hiring and retention efforts the past 6 years.

Other challenges to FDA's foreign drug inspection program remain. Unlike domestic drug inspections, most foreign drug firms receive advance notice of an FDA inspection. When FDA inspectors are traveling from the United States, which is the case in most foreign drug inspections, the FDA pre-announces inspections. Foreign drug firms generally get 12 weeks advance notice on when FDA inspectors are coming to their plants. The concerns raised by recent investigative reports is that this system gives plants ample time to clean up evidence of unsanitary conditions, wrongdoing, or data manipulation.

In 2014, to address these issues, the FDA instituted an initiative in India giving plants only short or no advance notice of inspections. As a result, the serious violations uncovered by inspectors rose by almost 60 percent. The initiative was discontinued in July 2015. FDA told the committee they discontinued the initiative because it lacked protocols and evaluation criteria. However, FDA still must believe there is value to short notice inspections, because they conduct such inspections in for-cause situations and conduct short notice inspections domestically.

Finally, in about 80 percent of inspections, FDA sends only one inspector, who is often reliant on the drug firm's employees or agents for translation. This solitary inspector, relying on the firm for translation and perhaps even travel arrangements, is allocated only a few days for the difficult task of inspecting a drug plant that can be the size of a small city. Meanwhile, the drug firm has about 3 months advance notice of the inspection. If the firm is unscrupulous, that is more than enough time to subvert regulations by fabricating records and concealing actual conditions.

Despite having the deck stacked against them, the committee has seen and heard plenty of accounts about intrepid FDA inspectors who have discovered serious misconduct at firms in India and China, protecting our Nation's drug supply in the process. We thank them for their service.

FDA needs to respond to the overall challenges of foreign drug inspections with more vigor. As they said in "Jaws," "You're going to need a bigger boat." We must maintain public confidence and trust in our drug supply, and FDA needs to rise further to meet the challenge. I welcome our witnesses and look forward to the testimony.

Ms. DEGETTE. Thank you so much, Mr. Walden.

The Chair now recognizes the chairman of the full committee, Mr. Pallone, for 5 minutes.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairwoman DeGette.

Today, the committee continues its longtime work of conducting oversight of the FDA's foreign drug inspection program. The program is a key piece of our efforts to ensure that the prescription drugs Americans take every day are safe and effective. Under the law, any firm, whether it's basically—whether it's based domestically or overseas, that seeks approval to market a drug in the U.S. must comply with the FDA's current good manufacturing practice regulations.

Both foreign and domestic firms are held to the same standards, which lay out the essential quality controls that ensure drugs are safe for use, and those standards also apply equally to both brand and generic manufacturers. While it's up to the manufacturers to take the necessary steps to implement the CGMP practices, FDA is tasked with inspecting facilities around the world to verify they're in compliance.

In the past, the committee found that FDA was woefully unprepared to take on the challenge of regulating and inspecting foreign drug manufacturers. As part of our ongoing oversight of this program, we found that foreign firms were not being inspected with regular frequency, and FDA had no permanent presence overseas, and its databases could not even tell what firms were actively shipping products to the United States.

And as a result of those disturbing issues, in 2012 Congress passed and the President signed the Food and Drug Administration Safety Innovation Act of 2012, and that law changed the way FDA selects firms to inspect, allowing it to focus on more high-risk facilities, including those abroad. It also increased FDA's authority over foreign manufacturers.

Then in 2013, the Drug Quality and Security Act provided FDA with track-and-trace authority to give the agency more tools to counter potentially dangerous drugs in the supply chain. And again in 2017, Congress provided more resources to FDA's foreign inspection program through the Generic Drug User Fee Amendment.

Now, despite these new authorities and resources, FDA's foreign drug inspection program continues to face challenges. For instance, the number in foreign inspections has actually declined the last 2 years. This is troubling because FDA had been making progress in inspecting more facilities, up until 2 years ago, and FDA also continues to struggle with hiring staff to conduct foreign inspections.

Again, this is all disturbing considering that Congress provided the generic drug user fees in part to fund foreign inspections. And I'm interested in hearing from the FDA on why the number of foreign inspections has declined in recent years and what's preventing them from reaching its capacity.

Now, today's hearing focuses on FDA's efforts, manufacturers have the responsibility to guarantee their products are safe and effective. We have to do what we can to ensure that manufacturers continue to produce high-quality drug products, including through innovative methods such as continuous manufacturing. Those methods not only help control quality but also enable firms to compete in the global market.

And this one final point I'd just like to keep in mind is that the issues we'll be discussing today affect all kinds of drugs throughout the supply chain. Much of the press coverage has framed these issues as a generic drug issue, but the fact is that the majority of active pharmaceutical ingredients for both generics and brands come from foreign countries.

Generic drugs have saved Americans billions of dollars and are critical to lowering healthcare costs across the board. FDA must ensure that any company, whether brand or generic, that wishes to market drug products in the U.S. adheres to the same quality standards. That not only provides a level playing field but confidence in American consumers that the drugs they're taking will be safe and effective.

So, again, I look forward to hearing from our witnesses about what's being done to ensure that confidence and what more is needed to secure the Nation's drug supply. And unless anybody wants my minute, I'm going to yield back. Thank you, Madam Chair.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Today, the committee continues its longtime work of conducting oversight of the Food and Drug Administration's foreign drug inspection program. This program is a key piece of our efforts to ensure that the prescription drugs Americans' take every day are safe and effective.

Under the law, any firm—whether it is based domestically or overseas—that seeks approval to market a drug in the United States must comply with FDA's Current Good Manufacturing Practice (CGMP) regulations.

Both foreign and domestic firms are held to the same standards, which lay out the essential quality controls that ensure drugs are safe for use. Those standards also apply equally to both brand and generic manufacturers. While it is up to the manufacturers to take the necessary steps to implement CGMP practices, FDA is tasked with inspecting facilities around the world to verify their compliance.

In the past, the committee found that FDA was woefully unprepared to take on the challenge of regulating and inspecting foreign drug manufacturers. As part of our ongoing oversight of this program, we found that foreign firms were not being inspected with regular frequency, FDA had no permanent presence overseas, and its databases could not even tell it what firms were actively shipping products to the United States.

As a result of these disturbing issues, in 2012, Congress passed and the President signed the Food and Drug Administration Safety and Innovation Act of 2012. The law changed the way FDA selects firms to inspect, allowing it to focus on more high-risk facilities, including those abroad. It also increased FDA's authorities over foreign manufacturers.

Then, in 2013, the Drug Quality and Security Act provided FDA with "track-and-trace" authority to give the agency more tools to counter potentially dangerous drugs in the supply chain. And, again in 2017, Congress provided more resources to FDA's foreign inspection program through the Generic Drug User Fee Amendments.

Despite these new authorities and resources, FDA's foreign drug inspection program continues to face challenges. For instance, the number of foreign inspections has declined the last 2 years. This is troubling because FDA had been making progress in inspecting more facilities up until 2 years ago. FDA also continues to struggle with hiring staff to conduct foreign inspections.

Again, this is all deeply disturbing considering that Congress provided the generic drug user fees, in part, to fund foreign inspections. I am interested in hearing from FDA on why the number of foreign inspections has declined in recent years and what is preventing it from reaching its capacity.

While today's hearing focuses on FDA's efforts, manufacturers have the first responsibility to guarantee their products are safe and effective. We must do what we can to ensure manufacturers continue to produce high-quality drug products, including through innovative methods such as continuous manufacturing. Those methods not only help control quality, but also enable firms to compete in the global market.

One final point to keep in mind is that the issues we will be discussing today affect all kinds of drugs throughout the supply chain. Much of the press coverage has framed these issues as a "generic drug issue"—but the fact is that the majority of active pharmaceutical ingredients (API) for both generics and brands come from foreign countries.

Generic drugs have saved Americans billions of dollars, and are critical to lowering healthcare costs across the board. FDA must ensure that any company, whether brand or generic, that wishes to market drug products in the United States adheres to the same quality standards. That provides not only a level playing field, but confidence in American consumers that the drugs they are taking will be safe and effective.

I look forward to hearing from our witnesses about what is being done to ensure that confidence, and what more is needed to secure the Nation's drug supply.

I yield back.

Ms. DEGETTE. The gentleman yields back.

The Chair now recognizes Mr. Guthrie for 5 minutes.

OPENING STATEMENT OF HON. BRETT GUTHRIE, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. GUTHRIE. Thank you, Chair DeGette, for holding this very important hearing.

The adequacy of FDA's oversight of the U.S. drug supply has been a longstanding issue for this committee. This committee has long been at the forefront of increasing access to reducing the price of drugs in the United States, particular in our effort to expand access to generic drugs.

Over the last three decades, the pharmaceutical industry has been globalized, and drug manufacturing has shifted significantly from the United States to overseas. Today, about 80 percent of ingredients for America's drug supply are manufactured overseas, and roughly 40 percent of drugs in the finished form are imported.

FDA has the responsibility to monitor the safety and effectiveness of drugs through inspections of drug manufacturing. Over the years, the Government Accountability Office has reported that the FDA has been slow to make recommended changes to the foreign drug inspection program in response to a globalized environment.

In 2012, this committee bolstered FDA's foreign drug inspections with additional authorities in the Food and Drug Administration Safety Innovation Act and funding through the Generic Drug User Fee Act. With this support, the FDA has increased the number of foreign drug inspections from 333 in 2007 to 935 in 2018. Through a recent agreement with the European Union on greater cooperation on drug inspections, the FDA has even more resources to focus drug inspections in high-risk facilities.

While important improvements have been made, FDA has persistent challenges. Past GAO reports and investigative reporting have raised concerns about the ability of FDA to oversee a globalized supply chain when 80 percent of the inspections involve only one inspector. Translation is often provided by the firm to be inspected, and most of the inspections are preannounced with firms getting 2 to 3 months' advance notice.

In contrast, domestic facilities are usually inspected without notice. These conditions are concerning because there have been notable cases of systematic falsification and deception by firms determined to subvert FDA regulations. Putting FDA at this kind of disadvantage against such misconduct is not acceptable, particularly when we're talking about drugs consumed by millions of Americans daily.

The FDA has known for decades about the need to globalize its foreign inspection program and operationalize it effectively. A strategy is needed to change the unbalanced dynamic where domestic facilities are usually inspected without notice, yet foreign facilities are given up to 3 months to prepare.

Despite the additional resources provided by user fees since 2013, it appears the FDA has a deficit of inspectors for several years. For staff based in the United States, FDA management should consider every tool available for creative hiring incentives and consult with other Federal agencies who effectively staff similarly situated personnel.

FDA getting direct-hire authority is a good start, but more must be done to increase hiring and, just as important, retain and promote inspectors who take on these responsibilities. With additional staff, FDA should increase the number of inspections conducted by teams rather than a single inspector and with translators independent of the firm being inspected.

Surveillance inspections are data-dependent, yet the potential for negligent or corrupt business practices overseas is well known. A trust-based inspection system must be closely evaluated to assess the true usefulness of data, information accepted at face value from the foreign-based facilities.

With the majority of drug ingredients in drugs being imported into the U.S., we are vulnerable to drug shortages, compromises in quality, and reliance on foreign sources. The question for FDA should not be how do we find solutions; instead, the question should be how quickly can we put solutions into action to continue to make sure America's drug supply is safe.

On another note, while I know it's not the direct focus of today's hearing, I want to emphasize that lowering drug prices is one of the top things I hear back home and one of my top priorities as a member of this committee. I am disappointed that this week we are going to go through—pursue partisan legislation on the floor instead of bipartisan policies that have broad support.

I look forward to working with my colleagues to advance bipartisan reform that will actually lower drug prices while preserving innovative research. The FDA must maintain the public's confidence in America's drug supply by ensuring it has a smart, effective foreign drug inspection program strategy that is not just planned or discussed but is both operational and successful. I welcome the witnesses, and I look forward to the testimony.

I yield back.

[The prepared statement of Mr. Guthrie follows:]

PREPARED STATEMENT OF HON. BRETT GUTHRIE

Thank you, Chair DeGette, for holding this very important hearing. The adequacy of FDA's oversight of the U.S. drug supply has been a longstanding issue for this Committee.

This committee has long been at the forefront of increasing access to and reducing the price of drugs in the United States, particularly in our efforts to expand access to generic drugs.

Over the last three decades, the pharmaceutical industry has become globalized and drug manufacturing has shifted significantly from the United States to overseas. Today, about 80 percent of ingredients for America's drug supply are manufactured overseas, and roughly 40 percent of drugs in the finished form are imported.

FDA has the responsibility to monitor the safety and effectiveness of drugs through inspections of drug manufacturing. Over the years, the Government Accountability Office (GAO) has reported that the FDA has been slow to make recommended changes to the foreign drug inspection program in response to a globalized environment.

In 2012, this committee bolstered FDA's foreign drug inspections with additional authorities in the Food and Drug Administration Safety and Innovation Act and funding through the Generic Drug User Fee Act. With this support, the FDA has increased the number of foreign drug inspections from 333 in 2007 to 935 in 2018. Through a recent agreement with the European Union on greater cooperation on drug inspections, the FDA has even more resources to focus drug inspections in high-risk facilities.

While important improvements have been made, FDA has persistent challenges. Past GAO reports and investigative reporting have raised concerns about the ability

of FDA to oversee a globalized supply chain when 80 percent of inspections involve only one inspector, translation is often provided by the firm to be inspected, and most of the inspections are preannounced, with firms getting 2 to 3 months advance notice. In contrast, domestic facilities are usually inspected without notice. These conditions are concerning because there have been notable cases of systemic falsification and deception by firms determined to subvert FDA regulations. Putting FDA at this kind of a disadvantage against such misconduct is not acceptable, particularly when we are talking about drugs consumed by millions of Americans daily.

The FDA has known for decades about the need to globalize its foreign inspection program and operationalize it effectively. A strategy is needed to change the unbalanced dynamic where domestic facilities are usually inspected without notice, yet foreign facilities are given up to 3 months to prepare.

Despite the additional resources provided by user fees since 2013, it appears that FDA has had a deficit of inspectors for several years. For staff based in the United States, FDA management should consider every tool available for creative hiring and incentives and consult with other Federal agencies who effectively staff similarly situated personnel. FDA getting direct hire authority is a good start, but more must be done to increase hiring and—just as important—retain and promote inspectors who take on these responsibilities.

With additional staff, FDA should increase the number of inspections conducted by teams rather than a single inspector, and with translators independent of the firm being inspected. Surveillance inspections are data-dependent, yet the potential for negligent or corrupt business practices overseas is well-known. A trust-based inspection system must be closely evaluated to assess the true usefulness of data and information accepted at face value from foreign-based facilities.

With the majority of drug ingredients and drugs being imported into the U.S., we are vulnerable to drug shortages, compromises in quality, and reliance on foreign sources. The question for FDA should not be "How do we find solutions?" Instead, the question should be "How quickly can we put solutions into action to continue to make sure America's drug supply is safe?"

On another note, while I know that this is not the direct focus of today's hearing, I want to emphasize that lowering drug prices is one of the top things I hear back home and one of my top priorities as a member of this committee. I am disappointed that my colleagues on the other side of the aisle have chosen to pursue partisan legislation on the floor this week instead of bipartisan policies that have broad support. I look forward to working with my colleagues to advance bipartisan reform that will actually lower drug prices.

The FDA must maintain the public's confidence in America's drug supply by ensuring it has a smart, effective foreign drug inspection program strategy that is not just planned or discussed but is both operational and successful. I welcome the witnesses and look forward to the testimony.

Ms. DEGETTE. The gentleman yields back.

I ask unanimous consent that the Members' written opening statements be made part of the record.

Without objection, so ordered.

I would now like to introduce our witnesses for today's hearing, Dr. Mary Denigan, who's the Director of Healthcare, Government Accountability Office. Welcome. And Dr. Janet Woodcock. We usually just have a reserved seat for you at all times, Dr. Woodcock. Thank you for being back with us today. She's the Director of the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.

Both of you are aware that the committee is holding an investigative hearing, and when doing so, we have the practice of taking testimony under oath. Do you have any objections to testifying under oath?

Let the record reflect the witnesses responded no.

The Chair then advises you that, under the rules of the House and the rules of the committee, you're entitled to be accompanied by counsel. Does either of you wish to be accompanied by counsel?

Let the record reflect the witnesses have responded no.

If you would, then, please rise and raise your right hand so you may be sworn in.

[Witnesses sworn.]

Ms. DEGETTE. Let the record reflect the witnesses have responded affirmatively, and you're now under oath and subject to the penalties set forth in title 18, section 1001 of the U.S. Code.

The Chair now will recognize our witnesses for a 5-minute summary of their written statements. In front of each of you is a microphone and timer and a series of lights. The timer will count down your time, and the red light will turn on when the 5 minutes has come to an end.

Now I'd like to recognize you, Dr. Denigan, for 5 minutes.

STATEMENTS OF MARY DENIGAN-MACAULEY, PH.D., DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE; AND JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

STATEMENT OF MARY DENIGAN-MACAULEY, Ph.D.

Dr. DENIGAN-MACAULEY. Chair DeGette, Ranking Member Guthrie, and members of the subcommittee, thank you for the opportunity to discuss preliminary findings from our ongoing work, examining FDA's foreign drug inspection program. It is imperative that Americans have access to safe and effective drugs, whether produced here or abroad. Today, the majority of brand-name, generic, and over-the-counter drugs are manufactured overseas, primarily in India and China. However, we have had longstanding concerns about FDA's ability to oversee the increasingly global supply chain.

In 1998, we reported the FDA had significant problems managing its foreign inspection data and conducted infrequent inspections of foreign establishments compared to their domestic counterparts. Since then, we have returned to the topic multiple times and found that many of these problems persist.

In 2008, for example, we determined that, because of inaccurate data, FDA did not know how many foreign drug establishments were subject to inspection. In addition, we found that FDA continued to inspect relatively few foreign establishments and that, when it did, investigators faced unique challenges that influenced how the inspections were conducted.

For example, unlike in the United States, where an establishment has no notice that an investigator is coming, FDA routinely gave foreign manufacturers significant notice. Further, FDA investigators had to rely on English-speaking employees of the very establishment that they were inspecting to translate, including key documents that demonstrated compliance with good manufacturing practices.

In 2010, we found that, while FDA was conducting more inspections overseas, many establishments had still never been inspected. We also identified shortcomings in the operations of the foreign offices that FDA opened in order to provide the agency with important in-country information and inspection capability. In 2010 and

again in 2016, we found that the offices faced persistently high vacancy rates, raising questions about their effectiveness.

As a result of these challenges, we added FDA's oversight of medical products, including drugs, to our high-risk series, citing FDA's inability to ensure the quality of drugs manufactured overseas as an area of particular concern.

This brings me to our current work. While the number of foreign drug inspections increased from 2012 to 2016, inspections have since dropped due to continued inaccuracies in data and investigator shortages. FDA is also still having trouble filling positions in foreign offices as well as positions for domestically based investigators who conduct the majority of these inspections overseas.

We also found that FDA still provides up to 3 months' advance notice for most foreign inspections, which gives establishments the opportunities to fix problems before the investigator arrives.

Further, investigators face persistent challenges when they travel overseas. As we learned on our site visits to India and China and in conversations with investigators based there and in the United States, lone investigators often had to inspect manufacturing campuses covering acres of land in rural areas. The majority have little flexibility to extend their time at a facility because travel schedules require back-to-back inspections.

In addition, FDA continues to send investigators into establishments without translators. This is particularly problematic in China, Japan, and South Korea. Investigators are left to rely on translators provided by the drug manufacturer that is being inspected, and there can be uncertainties about the accuracy of the information they receive. One investigator we spoke to said he had to resort to a translation app on their phone to conduct their work.

In closing, foreign manufacturers continue to be a critical source of drugs for millions of Americans, and FDA uses inspections as a key tool to ensure the quality of those drugs. FDA has made significant changes to adapt to the globalization of the drug supply chain and has greatly increased the number of inspections conducted overseas. However, the agency continues to face many of the same challenges that we identified in the past, raising questions about FDA's ability to conduct inspections overseas that are equivalent as required by law to those done here in the United States.

Thank you, Chair DeGette, Ranking Member Guthrie, and members of the subcommittee, for holding this important hearing and continuing your oversight. This concludes my remarks. I am happy to respond to any questions you may have.

[The prepared statement of Dr. Denigan-Macauley follows:]

United States Government Accountability Office

Testimony

Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
Expected at 10:00 a.m. ET
Tuesday, December 10, 2019

DRUG SAFETY

Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections

Statement of Mary Denigan-Macauley
Director, Health Care

GAO Highlights

Highlights of GAO-20-262T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

December 10, 2019

DRUG SAFETY

Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections

Why GAO Did This Study

More than 60 percent of establishments manufacturing drugs for the U.S. market were located overseas in fiscal year 2018. FDA has estimated that about 40 percent of finished drugs and 80 percent of active drug ingredients are manufactured overseas. 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 long-standing concerns about FDA's ability to oversee the increasingly global supply chain, an issue highlighted in GAO's High Risk Series for the last 10 years. 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) and 2016 (GAO-17-143) that FDA was conducting more of these foreign drug inspections, but GAO also reported that FDA may have never inspected many establishments manufacturing drugs for the U.S. market.

This statement is based on ongoing work and provides preliminary GAO observations on 1) the number of foreign inspections FDA has conducted, 2) inspection staffing levels, and 3) challenges unique to foreign inspections. For this work, GAO examined FDA data, visited FDA foreign offices in China and India, and interviewed drug investigators based in these offices and in the United States.

What GAO Recommends

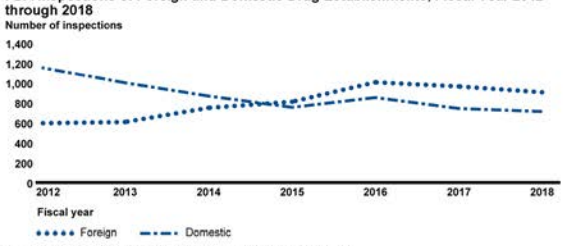
GAO will continue to assess these issues as part of ongoing work, and make recommendations as appropriate.

View GAO-20-262T. For more information, contact Mary Denigan-Macauley at (202) 512-7114 or deniganmacauleym@gao.gov.

What GAO Found

GAO's preliminary analysis of Food and Drug Administration (FDA) data shows that from fiscal year 2012 through 2016, the number of foreign drug manufacturing establishment inspections increased. From fiscal year 2016 through 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively. Howevever, the total number of foreign inspections surpassed the number of domestic inspections in 2015, and a growing percentage of FDA's foreign inspections (43 percent in 2018) were conducted in China and India, where most establishments that ship drugs to the United States were located. FDA officials attributed the decline, in part, to vacancies among investigators available to conduct inspections. GAO previously noted the vital role that inspections play in FDA's oversight of foreign establishments.

FDA Inspections of Foreign and Domestic Drug Establishments, Fiscal Year 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-262T

FDA has 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. FDA was in the process of 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 faces persistent vacancies among investigators in its foreign offices.

FDA investigators identified persistent challenges conducting foreign inspections, raising questions about the equivalence of foreign to domestic inspections. For example, while domestic inspections are almost always unannounced, FDA's practice of preannouncing foreign inspections up to 12 weeks in advance may give manufacturers the opportunity to fix problems. Investigators from FDA's China and India offices do conduct some unannounced inspections, but they are involved in a small percentage of inspections in these countries (27 percent and 10 percent, respectively). Further, FDA continues to rely on translators provided by the foreign establishments being inspected, which investigators said can raise questions about the accuracy of information FDA investigators collect.

Chair DeGette, Ranking Member Guthrie, and Members of the Subcommittee:

I am pleased to be here today to discuss our ongoing work on the Food and Drug Administration's (FDA) oversight of drugs manufactured overseas.[1] More than 60 percent of establishments manufacturing drugs—including brand-name, generic, and over-the-counter finished drugs and their active ingredients—for the U.S. market were located overseas in fiscal year 2018.[2] FDA is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are manufactured. FDA conducts several types of inspections of foreign manufacturing establishments, as testing a drug at the U.S. border cannot reliably determine whether the drug was manufactured in compliance with FDA regulations.[3]

[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 C.F.R. § 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 ongoing 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 C.F.R. § 600.3(h) (2019).)

[2]U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, *Report on the State of Pharmaceutical Quality: Assuring quality medicines are available for the American public*, (Silver Spring, Md.: May 2019), 3. We previously reported that nearly 40 percent of finished drugs and approximately 80 percent of active ingredients are manufactured overseas, according to FDA. See 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, D.C.: Dec. 16, 2016).

FDA defines manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 C.F.R. § 207.1 (2019). FDA defines an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.1 (2019).

[3]Establishments in foreign countries engaged in the manufacture, preparation, propagation, compounding or processing of drugs for importation into the United States are required to register annually with FDA. 21 U.S.C. § 360(i)(1). This registration information, along with registration information from domestic establishments, is maintained in FDA's drug registration database.

We have had long-standing concerns about FDA's ability to oversee the increasingly global supply chain, an issue highlighted in our High Risk Series.[4] In 1998, and again in 2008, we found that FDA inspected relatively few foreign drug manufacturing establishments—an estimated 8 percent of those subject to inspection for our 2008 report—and that challenges unique to foreign inspections influenced the manner in which FDA conducted such inspections.[5] In our 2008 report we recommended that FDA increase the number of foreign inspections it conducts, and FDA agreed with our recommendation.[6] We found in 2010, and again in 2016, 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, we also reported that many establishments manufacturing drugs for the U.S. market may never have been inspected by FDA.[7] In addition, in the summer of 2018, FDA began announcing recalls of blood pressure medications manufactured overseas and tainted with a potential carcinogen, raising further questions about FDA's oversight of foreign-manufactured drugs.[8]

My testimony today is based on our ongoing examination of FDA's foreign drug inspection program and provides preliminary observations on

1. the number of FDA's foreign inspections,
2. inspection staffing levels, and

[4]See GAO, *High-Risk Series: Substantial Efforts Needed to Achieve Greater Progress on High-Risk Areas*, GAO-19-157SP (Washington, D.C.: Mar. 6, 2019).

[5]See GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: 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, D.C.: Sept. 22, 2008).

[6]See GAO-08-970, 43. Following our recommendation, FDA 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.

[7]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, D.C.: Sept. 30, 2010) and GAO-17-143.

[8]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

3. any challenges unique to foreign inspections.

To develop our preliminary observations, we analyzed data from FDA's Field Accomplishments and Compliance Tracking System, which contains information on inspections of drug manufacturing establishments. Specifically, we examined FDA data from fiscal year 2012 through fiscal year 2018 to determine: (1) the number of foreign and domestic inspections conducted by FDA, (2) the type of inspections, (3) the country in which the inspections took place, and (4) inspection results.[9] This date range was selected to allow for an analysis of trends over time through 2018, the last full fiscal year of data available when we began our analysis. To assess the reliability of these data, we reviewed related documentation, interviewed knowledgeable agency officials, conducted electronic data testing for missing data and outliers, and compared the data to published information from the same database. On the basis of these steps, we found these data sufficiently reliable for the purposes of our reporting objectives. We also visited FDA's foreign offices in China and in India, the countries where FDA performs the largest number of foreign drug inspections and which are FDA's offices that have drug investigators who conduct inspections—a unique aspect of these offices. At these two offices we interviewed a nongeneralizable selection of the six FDA drug investigators available in the offices at the time of our visits about their inspection efforts. (We plan to interview the remaining drug investigators deployed to these offices as part of our ongoing work.) While in those countries, we also accompanied investigators to two drug manufacturing establishments to observe inspection procedures. We also interviewed all 12 members of FDA's calendar year 2019 cadre of investigators who are based in the United States but exclusively conduct foreign drug inspections. Finally, we reviewed information from FDA on their inspection staffing levels since our last report in 2016.

The ongoing work on which this statement is based is being conducted in accordance with generally accepted government auditing standards.

[9]Our analysis focused on inspections related to the drug approval process or inspections conducted to determine an establishment's ongoing compliance with laws and regulations in the manufacture of human drugs already marketed in the United States. FDA conducts additional drug inspections that are beyond the scope of our review, such as to determine whether drug manufacturers are submitting to FDA, as required, complete and accurate data on adverse drug experiences associated with marketed drugs, inspections conducted for the President's Emergency Plan for AIDS Relief, and inspections of clinical trial sites, compounding pharmacies, and medical gas manufacturers.

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 and finished dosage forms—are manufactured throughout the world. According to a May 2019 FDA report, in fiscal year 2018 about 40 percent of establishments manufacturing drugs for the U.S. market were located domestically and more than 60 percent of establishments manufacturing for the U.S. market were located overseas.[10] As of March 2019, FDA data show that India and China had the most manufacturing establishments shipping drugs to the United States, with about 40 percent of all foreign establishments in these two countries. (See fig. 1.)

[10]U.S. Food and Drug Administration, *Report on the State of Pharmaceutical Quality*, 3.

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-20-262T

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

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.[11]

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.[12]

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-20-262T

[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.

[11]CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. See 21 C.F.R. pts. 210, 211, 212 (2019). FDA considers nearly all drug establishment inspections to include an assessment of CGMPs.

[12]Most combined inspections occur when FDA conducts a surveillance inspection at an establishment where a preapproval inspection was also being conducted.

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 an establishment catalog monthly. The catalog is 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.[13] 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 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. 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.[14]

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 experience 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.[15] 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, according to FDA officials, ORA staff may shift the order of establishments to be inspected

[13]GAO-08-970.

[14]See GAO-10-961 and GAO-17-143.

[15]Establishments may also be selected for surveillance inspections for other reasons, such as FDA's focus on a particular product.

on CDER's prioritized list based on geographic proximity to other planned inspection trips.

FDA Inspection Workforce

Investigators from ORA and, as needed, ORA laboratory analysts with certain expertise are responsible for inspecting drug manufacturing establishments.[16] 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, including 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.[17] 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.

[16]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.

[17]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.

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).[18] 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.

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.[19] 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

[18]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/

[19]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.

States.[20] 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.

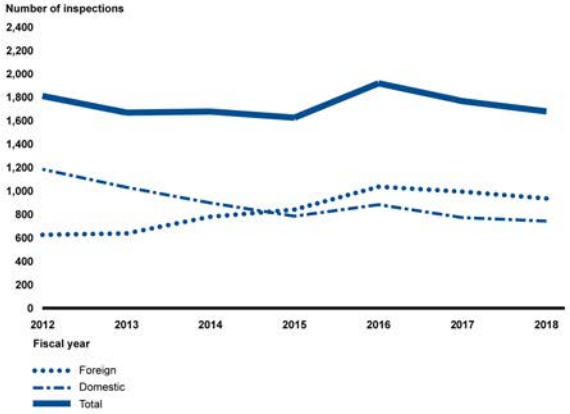
The Number Of Foreign Inspections Declined In Recent Years, And The Majority Of Such Inspections Identified Deficiencies

Total Number of FDA Foreign Drug Inspections Has Decreased Since Fiscal Year 2016 after Several Years of Increases

Our preliminary analysis of FDA data shows 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 (see fig. 2). In fiscal year 2015, the total number of foreign inspections surpassed the number of domestic inspections. From fiscal year 2016 to 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively.

[20]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.

Figure 2: Total Number of FDA Inspections of Foreign and Domestic Drug Establishments, Fiscal Year 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-262T

Note: The total number of inspections includes those conducted for preapproval, surveillance, and for-cause purposes.

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, 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 has pursued an initiative to inspect approximately 1,000 foreign establishments that lacked an inspection history and, as of November 2019, officials said all of these establishments had either been inspected or were determined to

not be subject to inspection.[21] 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).[22] 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. 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 FDA maintains about foreign establishments and the application of its risk-based site selection process.

FDA continues 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 (when we last reported on this issue) 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.

[21]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.

[22]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.

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-20-262T

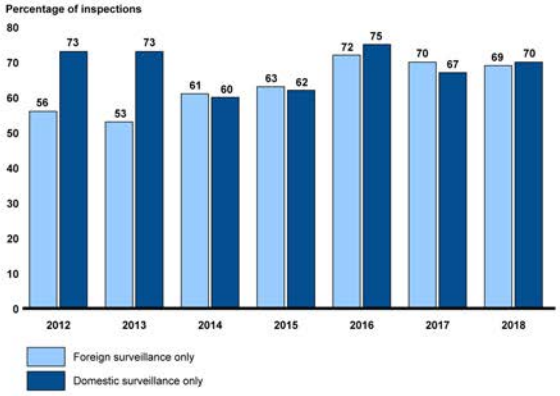
Note: The total number of inspections includes those conducted for preapproval, surveillance, and for-cause purposes.

Most Foreign Inspections Are Surveillance Inspections

Our preliminary analysis of FDA data shows 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 3 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).[23]

[23]See GAO-08-970, 27.

Figure 3: 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-20-262T

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.

FDA has 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 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.[24]

FDA Identified Deficiencies during the Majority of Foreign Inspections

Our preliminary analysis of FDA data shows 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.

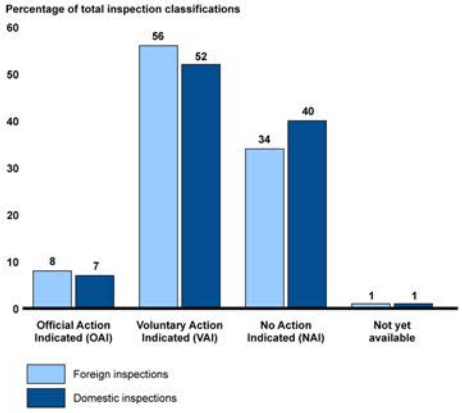
Source: GAO. | GAO-20-262T

About 59 percent of domestic inspections (3,702 out of 6,291) identified deficiencies during this time period. (See fig. 4.) 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.[25]

[24]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.

[25]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 4: 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-20-262T

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 preliminary 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. For example:

- **Failure to maintain the sanitation of the buildings used in the manufacturing processing, packing, or holding of a drug product (21 C.F.R. § 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 C.F.R. § 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 penicillin 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.

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.

Some investigators who conduct foreign inspections expressed concern with instances in which ORA or CDER reviewers reclassify the investigator's initial inspection classification recommendations of OAI to the less serious classification of VAI. We plan to examine this issue as part of our ongoing work.

FDA Continues To Face Challenges Filling Vacancies Among Staff Conducting Foreign Inspections

Our ongoing work showed FDA's foreign inspection workforce has staff vacancies, which FDA officials said contributed to the recent decline in inspections. As previously mentioned, FDA uses 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.[26] However, each of these groups has current vacancies. According to FDA officials, the agency is 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 conducts 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.[27] 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.[28] 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. 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.[29] 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 recently filled several of the vacancies, officials

[26]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.

[27]Inspections can be conducted by one investigator or multiple investigators. Therefore, investigators from more than one group could be involved with a single inspection.

[28]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.

[29]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.

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. According to FDA officials, the agency is attempting to fill these positions from the current ORA investigator pool, but officials are not confident that all 20 slots will 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 are those based in the China and India foreign offices—the countries where most drug inspections occur— and also include those on temporary duty assignment to these offices.[30] 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.[31] 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).

FDA has taken steps to address vacancies in the foreign offices, but continues to face challenges. In our 2010 report, we recommended that FDA develop a strategic workforce plan to help recruit and retain foreign office staff.[32] FDA released such a plan in March 2016, but the long-

[30]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.

[31]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, D.C.: Sep. 30, 2010), and GAO-17-143.

[32]GAO-10-960.

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.[33] According to this official, FDA investigators do not usually receive first priority for the training. FDA estimates that it can take as little as 1 year to over 2 years 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.

[33]We have highlighted timeliness concerns with the government-wide personnel security clearance process in our High Risk series. See GAO-19-157SP.

Persistent Challenges Unique To Foreign Inspections Raise Questions About Their Equivalence To Domestic Inspections

Our preliminary analysis indicates that FDA continues to face unique challenges when inspecting foreign drug establishments—as compared to domestic establishments—that raise questions about the equivalence of these inspections. Specifically, based on our interviews with drug investigators in the dedicated foreign drug cadre and 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.[34]

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.[35] Domestic drug establishment inspections 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 establishment's assistance to make travel arrangements, and ensure the safety of investigators when traveling in country.

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.[36] 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).

[34]GAO-08-970.

[35]GAO-08-970.

[36]According to FDA officials, FDA plans to add a new variable to its data to identify preannounced and unannounced inspections.

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, 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
Domestic 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: • 75 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-20-262T

[a]These percentages add up to over 100 percent as some inspections may involve more than one type of investigator.

Our preliminary work indicates 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 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. 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, 12 said that unannounced inspections are generally preferable to preannounced inspections. One investigator told us that, although they believe the best way to ensure industry compliance to CGMPs is for establishments to not know when FDA is coming for an inspection, there is no data that would allow the agency to evaluate whether unannounced inspections are better than preannounced inspections. In addition, some investigators told us that it is still possible to identify serious deficiencies during preannounced inspections. For example, investigators can 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 can 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. Our preliminary work indicates 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.[37] 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 is less of a challenge for inspections conducted in other foreign countries, including India and countries in Europe, because workers at establishments in these countries are more likely to speak English, and documentation is 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 needs to rely on translation.

[37] GAO-08-970.

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 is more risk of conflict of interest if the establishment uses 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 this 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 that 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 are 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. We will continue to examine this issue with FDA as part of our ongoing work.

Lack of Flexibility. Our preliminary work indicates 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.[38] Eight of the 12 dedicated foreign drug cadre investigators that we interviewed 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

[38]GAO-08-970.

involve three different countries.[39] 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 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.[40] 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. From fiscal years 2012 to 2018, the majority of both foreign and domestic

[39]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.

[40]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.

inspections were conducted by one person—77 percent and 66 percent, respectively.[41]

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).[42] 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 inspection reports.[43] 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 preliminary work indicates that the post-inspection reporting time frames can create challenges for domestic investigators that conduct foreign inspections and raise questions about the equivalence to domestic inspections. Eight of the 18 investigators that we interviewed 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

[41]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.

[42]Pub. L. No. 115-52, §§ 301, 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.

[43]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.

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, 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 drug supply chain and has greatly increased the number of inspections that it conducts of foreign establishments. Notably, it has markedly increased the percentage of foreign inspections conducted to monitor drugs already on the market, which we previously noted were vital to FDA oversight of foreign establishments. However, the agency continues to be faced with many of the same challenges in the oversight of foreign establishments that we identified in our 2008 report. Our preliminary work has identified inspection decreases, related in part to FDA challenges filling investigator vacancies. We have also identified a variety of unique challenges that investigators face in foreign inspections. As we continue to conduct our work, we will further examine the cumulative effect of these challenges that raise questions about FDA's ability to conduct equivalent inspections in foreign establishments. We will examine the extent to which FDA has assessed its oversight of drugs manufactured overseas and the steps it is taking to mitigate any risks, and make recommendations as appropriate.

Chair DeGette, Ranking Member Guthrie, and Members of the Subcommittee, this completes my prepared statement. I would be pleased to respond to any questions that you may have at this time.

GAO Contact and Staff Acknowledgments

If you or your staff have any questions about this testimony, please contact Mary Denigan-Macauley, Director, Health Care at (202) 512-7114 or DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. GAO staff who made key contributions to this testimony are William Hadley (Assistant Director); John Lalomio (Analyst-in-Charge); Katherine L. Amoroso; George Bogart; Zhi Boon; Derry Henrick; Laurie Pachter; and Vikki Porter.

GAO's Mission	The Government Accountability Office, the audit, evaluation, and investigative arm of Congress, exists to support Congress in meeting its constitutional responsibilities and to help improve the performance and accountability of the federal government for the American people. GAO examines the use of public funds; evaluates federal programs and policies; and provides analyses, recommendations, and other assistance to help Congress make informed oversight, policy, and funding decisions. GAO's commitment to good government is reflected in its core values of accountability, integrity, and reliability.
Obtaining Copies of GAO Reports and Testimony	The fastest and easiest way to obtain copies of GAO documents at no cost is through our website. Each weekday afternoon, GAO posts on its website newly released reports, testimony, and correspondence. You can also subscribe to GAO's email updates to receive notification of newly posted products.
Order by Phone	The price of each GAO publication reflects GAO's actual cost of production and distribution and depends on the number of pages in the publication and whether the publication is printed in color or black and white. Pricing and ordering information is posted on GAO's website, https://www.gao.gov/ordering.htm. Place orders by calling (202) 512-6000, toll free (866) 801-7077, or TDD (202) 512-2537. Orders may be paid for using American Express, Discover Card, MasterCard, Visa, check, or money order. Call for additional information.
Connect with GAO	Connect with GAO on Facebook, Flickr, Twitter, and YouTube. Subscribe to our RSS Feeds or Email Updates. Listen to our Podcasts. Visit GAO on the web at https://www.gao.gov.
To Report Fraud, Waste, and Abuse in Federal Programs	Contact FraudNet: Website: https://www.gao.gov/fraudnet/fraudnet.htm Automated answering system: (800) 424-5454 or (202) 512-7700
Congressional Relations	Orice Williams Brown, Managing Director, WilliamsO@gao.gov, (202) 512-4400, U.S. Government Accountability Office, 441 G Street NW, Room 7125, Washington, DC 20548
Public Affairs	Chuck Young, Managing Director, youngc1@gao.gov, (202) 512-4800 U.S. Government Accountability Office, 441 G Street NW, Room 7149 Washington, DC 20548
Strategic Planning and External Liaison	James-Christian Blockwood, Managing Director, spel@gao.gov, (202) 512-4707 U.S. Government Accountability Office, 441 G Street NW, Room 7814, Washington, DC 20548

Ms. DEGETTE. Thank you, Doctor.

Dr. Woodcock, you're now recognized for 5 minutes.

STATEMENT OF JANET WOODCOCK, M.D.

Dr. WOODCOCK. Thank you.

Well, around the turn of the century, pharmaceutical manufacturing began to move out of the U.S., as people have already stated, but FDA was slow to react to this change. The agency had a longstanding inspectional organization called the Office of Regulatory Affairs, or ORA, that was organized around domestic sites that were called districts, and these districts inspected facilities, whether they had foods, drugs, devices, or whatever, within the boundaries of each district. And then they would volunteer inspectors to go outside of the U.S. from those districts.

FDA also had very poor and inaccurate data systems. So, unless a foreign site was part of an application in which it was overtly brought to FDA's attention, then it might not get inspected. And also in the data systems, there was a huge number of incorrect and duplicate sites. So the GAO said we had all these thousands we hadn't inspected. Many of them didn't really exist or they were duplicates of another site, but we didn't have data systems that could identify that.

As detailed in my testimony, by 2005, FDA was taking steps to rectify the situation. Center for Drugs began requesting more and more ex-U.S. GMP surveillance inspections, other than just the preapproval inspections that had been going on, using a risk-based model for site selection. Despite this, the ORA, the field organization, was hampered by the requirement for every 2-year domestic GMP inspections with no statutory requirement for ex-U.S. establishments.

Much of this changed, as people said, in 2012 when Congress passed FDASIA and the generic drug user fee program. FDASIA removed the 2-year domestic requirement and replaced it with a risk-based global approach to inspections. GDUFA provided ORA with additional resources to inspect the generic industry in both domestic and foreign.

At this time, FDA also took major changes in how we regulate pharmaceutical quality. I personally led a major, major reorganization of the Center for Drugs' quality function. And I assumed the role of Acting Director of an office—a newly formed Office of Pharmaceutical Quality. We cleaned up the inventory, creating the current site catalog that has lists of the existing firms that import drugs into the United States as well as the U.S. firms that make drugs for the U.S.

We established the Office of Surveillance inside the Office of Pharmaceutical Quality. The whole point of surveillance office is to surveil the inventory, and we can get into that later, but their job is to make sure we're looking at everything and what—and do trend analysis. And we established clear responsibilities between the Office of Compliance and other offices in CDER.

Subsequently, the Office of Regulatory Affairs undertook a major reorganization, the first in an extremely long time, and they established inspectorates along product lines, so now we have a drug inspectorate, right, rather than having districts that do everything.

They developed new SOPs called the Concept of Operations that established a uniform process for doing inspections both foreign and abroad for drugs.

As a result of all these changes, by 2016, foreign surveillance inspections had exceeded domestic, and this trend continues, as shown in the testimony. There had been a large uptick and warning letters as previously uninspected sites that were identified by the GAO and by our catalog were evaluated. FDA's really currently up to date on our sites. We know there are always new sites coming in. We assign them inspections, and we are on top of all these sites as in the—documented in the testimony. We expect performance of sites in India and China to improve as they're subjected to continued U.S. oversight.

Despite this, there is much more to do, including hiring inspectors and foreign office personnel—this is under way—transforming the site selection model into a true quantitative predictive model, but that will require data, us getting data, rather than PDF, which is what we get now, stimulating advanced manufacturing, and standardization and internationalization of quality standards. And finally, as we put in our shortage report, we're suggesting recognizing quality maturity as an important factor in manufacturers' production.

Happy to answer questions. Thank you.

[The prepared statement of Dr. Woodcock follows:]

TESTIMONY

OF

JANET WOODCOCK, MD
DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES

"SECURING THE U.S. DRUG SUPPLY CHAIN: OVERSIGHT OF FDA'S FOREIGN INSPECTION PROGRAM"

DECEMBER 10, 2019

RELEASE ONLY UPON DELIVERY

Chair DeGette, Ranking Member Guthrie, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS).

Today I 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. I 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). I 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 traditional 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 United States, first to Puerto Rico in response to tax incentives, and then to Europe and developing nations 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 United States 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 CDER's Site Catalog ("Catalog"), which lists all drug manufacturing facilities worldwide that are subject to routine FDA inspections.[3] As of August 2019, 28 percent of facilities manufacturing APIs and 47 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the United States. **(See Figures 1 and 2)**

[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.

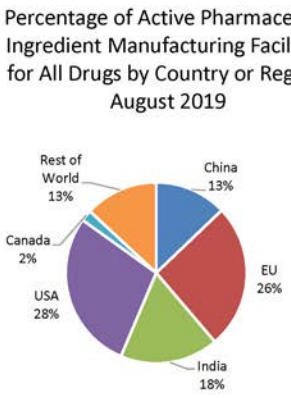


Figure 1: For all FDA-regulated drugs, 28 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

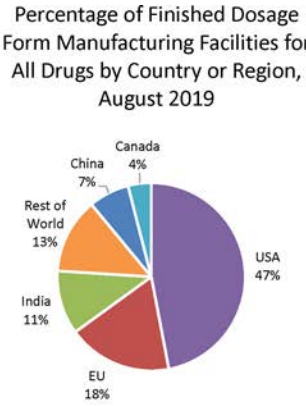


Figure 2: For all FDA-regulated drugs, 47 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

This movement accelerated in the 2000s, but due to mandates for 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 (P.L.112-144), the Agency was legally required to inspect manufacturing facilities in the United States every two years but had no similar mandate for the inspection frequency of foreign facilities. This resulted in more frequent inspections for domestic facilities and created an unequal playing field that was exacerbated by resource constraints.

The Globalization of FDA's Drug Inspection Program

In response to the move from domestic to global manufacturing and the passage of FDASIA, 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.

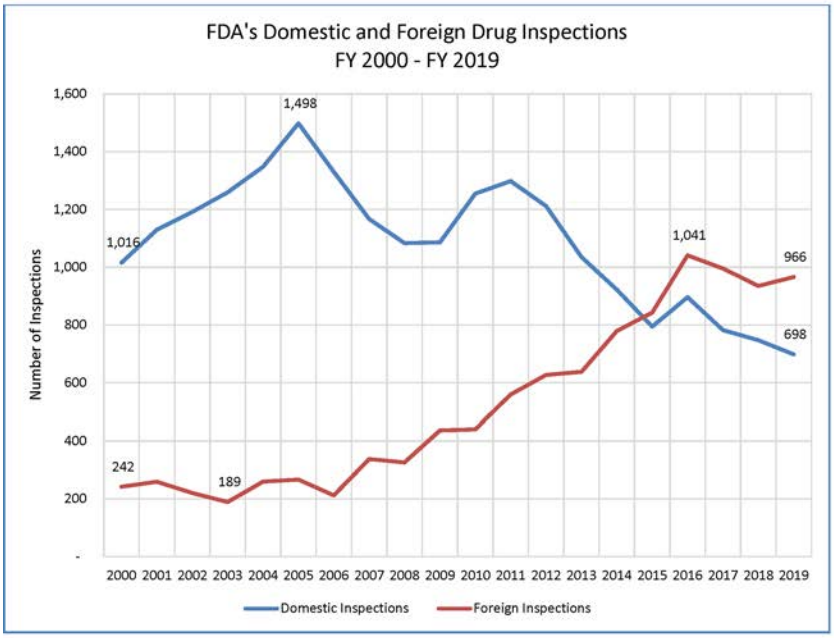


Figure 3: FDA's Inspections of Foreign Drug Manufacturing Facilities Increased Sharply After 2006 and Have Exceeded Inspections of Domestic Drug Facilities Since 2015

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, periodically, 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 announces international surveillance inspections.[4] 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.

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.

[4] FDA usually announces international surveillance inspections in advance, partly due to logistics such as arranging travel and access to facilities, and securing visas, and partly because of the high costs of conducting foreign inspections. When a surveillance inspection is announced, some manufacturers conduct a self-inspection or hire an independent inspector to ensure that manufacturing processes meet requirements.

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."[5] The Agency thanks this committee and Congress for your support in enacting this law.

In 2007, FDA began to shift its investigator workforce to cover foreign facilities and to rebalance allocation between domestic and foreign inspections. Still, the Agency did not have adequate staffing and financial resources for foreign inspection coverage. 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 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. CDER's Catalog showed that as of July 2016, there were 965 foreign manufacturing facilities that had never been inspected by FDA. By the end of FY 2019, FDA had inspected 495 or 51 percent of these previously uninspected facilities **(See Figure 4)**. An additional 359 facilities (37 percent) were removed from the Catalog because they were no longer part of FDA's inspection obligations for a number 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 six percent of the facilities had refused inspection;[6] 37 or four percent of the facilities were inaccessible to FDA investigators because they were unable to travel to them (e.g., as

[5] The Federal Food, Drug, and Cosmetic Act (FD&C Act) describes different circumstances in which a drug may considered adulterated. For example, a drug might be 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).

[6] Under the FD&C Act, as amended by FDASIA, a drug product will be deemed adulterated if a drug 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.

a result of travel warnings); and 22 or two percent had no drug shipments.

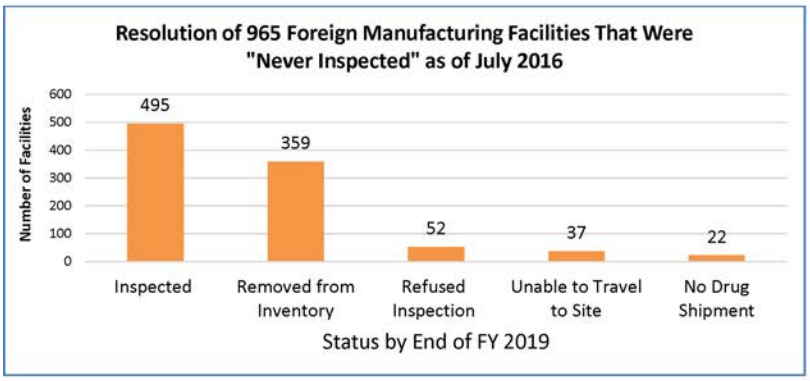


Figure 4. FDA has now inspected 495 (51%) of the 965 foreign manufacturing facilities that had never been inspected, as of July 2016.

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 conducted from December 2011 to June 2019, 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)**

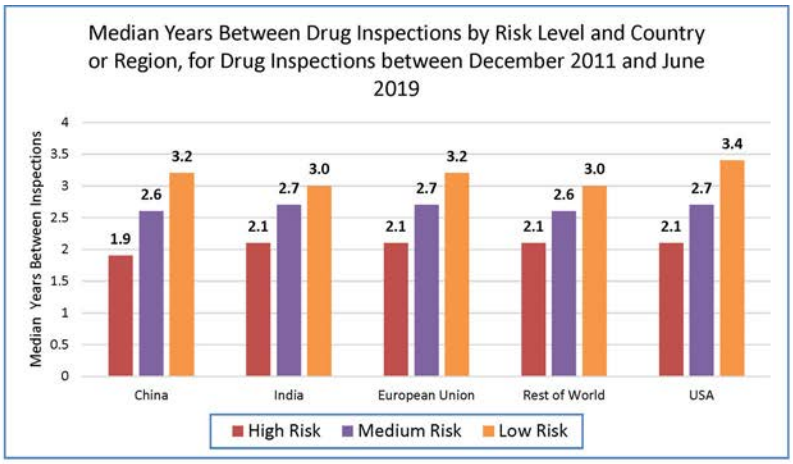


Figure 5. FDA inspected high-risk manufacturing facilities more frequently than medium- or low-risk facilities, and medium-risk facilities more frequently than low-risk facilities, across all countries or regions. In general, all facilities in a risk category were inspected with about the same frequency, 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 some deficiencies, particularly in foreign facilities that had not been inspected as frequently as domestic ones prior to the inception of FDASIA and GDUFA. 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).**

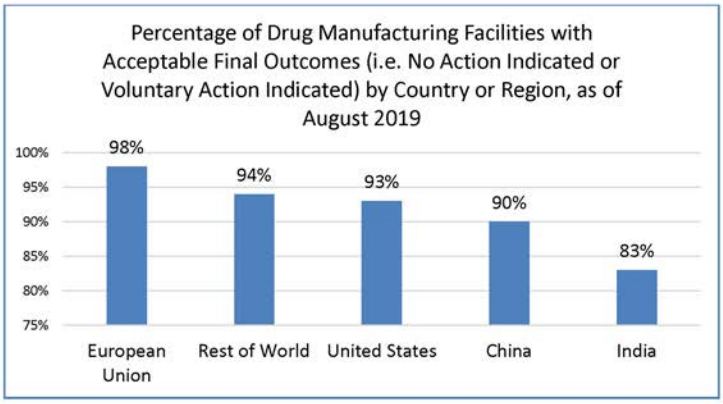


Figure 6. The majority of final inspection outcomes for manufacturing facilities making human drugs were acceptable, meaning that they were classified as having No Action Indicated or Voluntary Action Indicated. However, India had a lower percentage of acceptable outcomes than other countries and regions. (These were outcomes as of August 2019 for the most recent inspection of facilities that were in the Catalog as of July 2019.)

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

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

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 to prevent drugs from the facility from legally entering the United States. 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. Under our current authorities, foreign-based manufacturers of certain drugs can legally ship drugs to the United States without ever having been inspected by FDA. Drugs in this category typically include OTC monograph drugs and APIs used in pharmacy compounding. This increases the risk of exposing American patients to unsafe or ineffective drugs and requires resource-intensive efforts on FDA's part to identify and respond to any problems that arise subsequently. For example, last month, we issued a warning letter to a discount retailer for receiving OTC drugs produced by foreign manufacturers with serious violations of CGMPs. The majority of the foreign facilities involved had distributed drugs to the United States 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: the Office of Regulatory Affairs (ORA), which contains the field force of investigators who conduct

[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.

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

the inspections, and CDER, which includes compliance officers who review inspection reports that are initially recommended as OAI and for-cause inspections to determine the final classification and whether appropriate regulatory action is required. CDER also includes reviewers who evaluate applications for marketing approval and post-marketing changes. ORA has recently completed a multi-year effort to implement a specialized inspectorate focused on human drugs.

On June 6, 2017, CDER and FDA's Office of Regulatory Affairs (ORA) entered into a Concept of Operations[10] (ConOps) agreement to better integrate facility evaluations and inspections for human drugs. The planning for this integration began in 2013 in a Program Alignment initiative.[11] The ConOps is designed to improve the collaboration between ORA and CDER and enhance the efficiency and effectiveness of FDA's oversight of drug manufacturing facilities. As part of this effort, FDA redesigned processes to enhance the efficiency and effectiveness of classifications of inspection classifications **(See Figure 7)**. If ORA initially recommends classifying the inspection report as OAI, CDER's Office of Compliance then reviews the report and the manufacturing facility may submit a remediation plan to rectify any quality problems that were noted. CDER evaluates the evidence supporting inspection observations, impacts to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. Depending on the particular circumstances, including remediation efforts made at the facility, CDER may reclassify the inspection.

[10] See *https://www.fda.gov/media/107225/download.*
[11] See *https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora.*

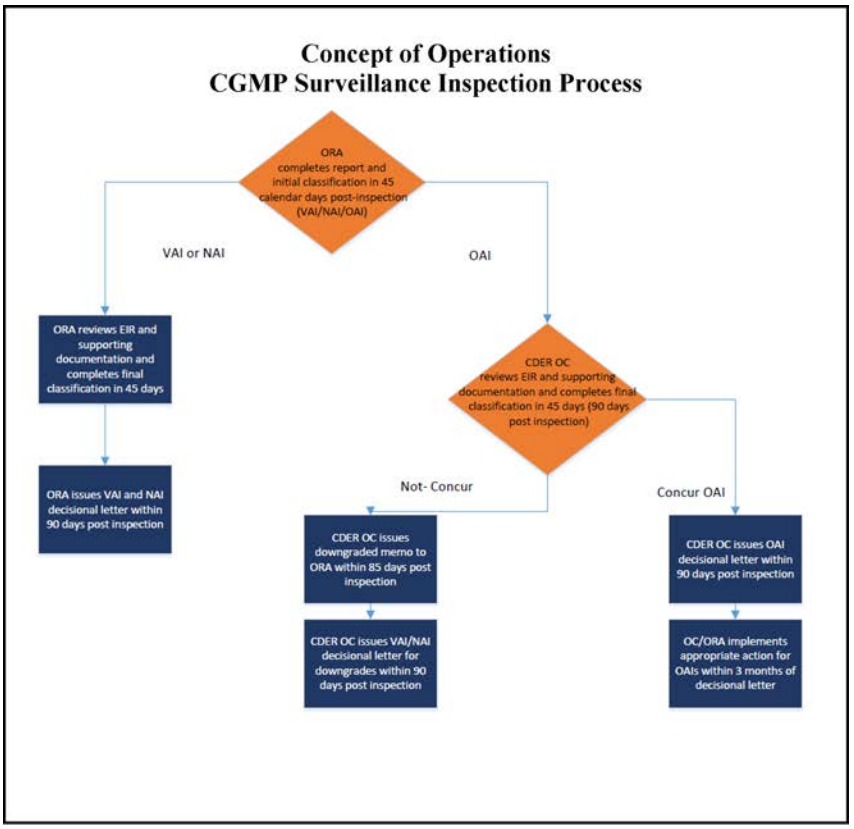


Figure 7. Process for classifying surveillance inspection outcomes after implementation of the ConOps.

Implementation of the ConOps has helped improve consistency in evaluation of inspection observations, classification of the inspection, 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.

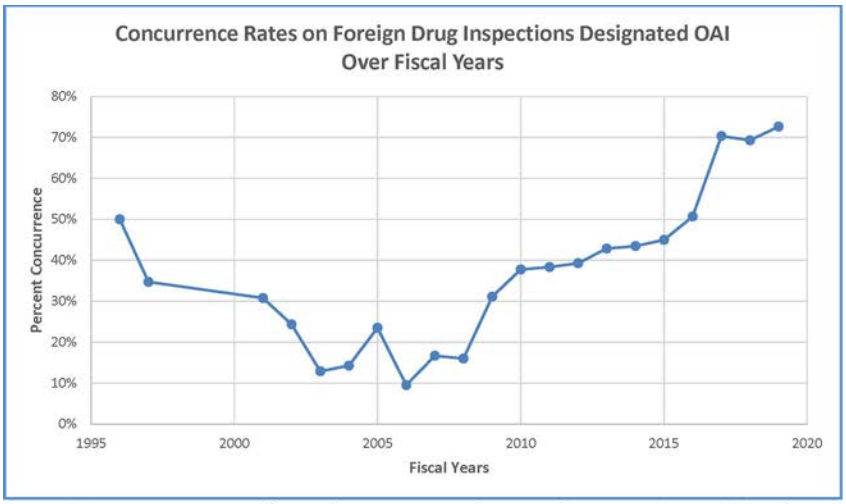


Figure 8. Concurrence rates on foreign drug inspections designated OAI were 50% in 1996 and rose to 73% in 2019. (FY 1996-1997 based on GAO data, all other data from FDA compliance database.)

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)**.

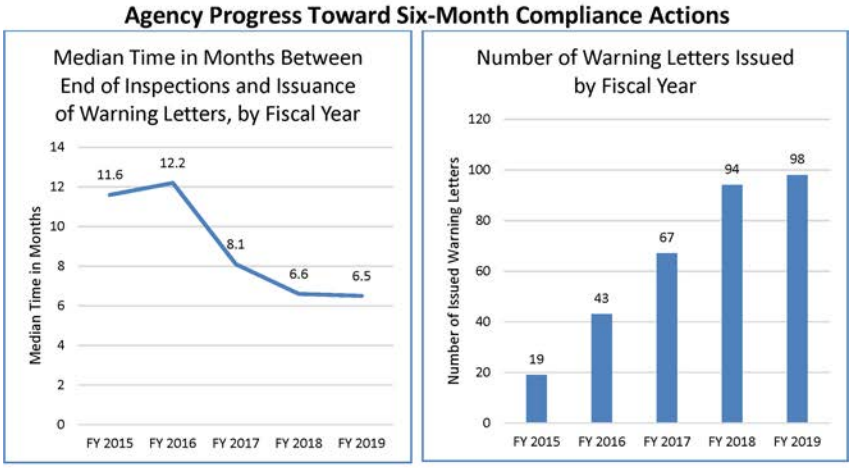


Figure 9. From FY 2015 to FY 2019 there has been an overall median 44% improvement in median time between the end of an inspection and issuance of a warning letter. During the same time, the number of warning letters increased.

Building an Investigator Work Force

FDA has performed more foreign than domestic inspections since 2015. The Agency utilizes a risk-based site selection model to identify firms for inspection. FDA has achieved this level of foreign coverage 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 investigators who inspect facilities manufacturing human drugs **(See Table 1)**. The majority of foreign inspections are performed by domestically based staff in the first two categories.

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	12 (included in the 188 listed above)	16 -18 inspections per year	16% (part of the 90% above)
Foreign Office-Based Investigators	12	15 inspections per year	10%

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

By the end of this calendar year we expect 20 pharmaceutical investigators will be onboarding, and with our new direct hire authority we anticipate filling all our pharmaceutical investigator vacancies in 2020. In recent years, FDA 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.

However, the Agency continues to face challenges in developing the investigator work force due to the rigorous nature of the job (e.g., foreign travel restrictions and hardship). Competition for qualified candidates in a low-unemployment economy adds to our challenge in hiring. Even if 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. Beyond these general issues, FDA faces specific challenges to achieving optimum staffing levels, such as negotiated agreements with host countries that affect the number of investigators who can be permanently attached to a foreign office.

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 United States, 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 raised the question of why we do not test every drug product before it enters the United States. 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.[12] 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[13]) and the current approach is effective and efficient.

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

[12] These are established by USP, see *https://qualitymatters.usp.org/what-usp-standard*.
[13] IQVIA. National Sales Perspective. 2014-2018. Extracted: August 2019.

supply disruptions.

Even when a firm does invest in such improvements, it may be difficult to identify measures of quality that could be used to predict major quality issues that can lead to shutdowns of manufacturing lines resulting in supply disruptions. Even if these measures were readily available, FDA might not have access to the needed data regarding the performance of the manufacturing facility.

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.[14] 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",[15] a way to create incentives for manufacturers to invest in product quality is to develop and implement a rating system for quality

[14] Fnhr, Ted, et al., 2015, Flawless-from Measuring Failure to Building Quality Robustness in Pharma, McKinsey & Company.
[15] *https://www.fda.gov/drugs/drug-shortages/agency-drug-shortages-task-force*.

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.

Conclusion

Over the past 20 years, the pharmaceutical industry that supplies American patients with drugs has, to a signficiant degree, moved offshore, so that today the majority of API and FDF manufacturing facilities are located outside the United States. In response, FDA has developed a risk-based approach to surveillance inspections that ensures equal treatment of foreign and domestic facilities. We believe that this is an effective and efficient approach for ensuring that American patients have access to a supply of safe and effective drugs. We thank the committee for the legislation that has made this transition possible. At the same time, the reliability of our drug supply chain could be further strengthened by investment in modern manufacturing technology and in establishing mature quality management systems in manufacturing facilities.

Ms. DEGETTE. Thank you so much, Dr. Woodcock.

It's now time for Members to ask questions, and the Chair will recognize herself for 5 minutes.

And one of the reasons why we do hearings like this on a continual basis is so that we can monitor these difficult issues over time. And this committee, as I said in my opening statement, has been working on foreign drug inspections for several decades now.

It seems to me, Dr. Denigan, after hearing your testimony, some of the—number one, we've made a lot of progress over the years, and Dr. Woodcock talked about some of that progress that we've made, but we still have some sort of stubborn issues that continue. And, listening to your testimony, it seems like some of them are, number one, we're giving advance warning to these facilities before we go; number two, we have problem getting independent translators to come, so we don't know about the reliability of what our inspectors are being told; number three, unique challenges of staffing with overseas inspections; and number four, the quality of data.

Are those some of the issues that you had identified?

Dr. DENIGAN-MACAULEY. Yes, that's correct.

Ms. DEGETTE. And, Dr. Woodcock, what's your view of issues like that that just continue to be difficult to address?

Dr. WOODCOCK. There are tradeoffs on many of these. Obviously, we'd like to be fully staffed, but the entire FDA has suffered some administrative problems with hiring, and many of the centers are down in personnel. The field has recently received direct-hire authority. They hope to bring on 20 people that they're onboarding, and then we'd hope to hire——

Ms. DEGETTE. Twenty people to do foreign inspections?

Dr. WOODCOCK. Well, they will—first, they'll have to get trained to be inspectors, right?

Ms. DEGETTE. OK.

Dr. WOODCOCK. And then some of them will reach the ability to become foreign inspectors. They hope to bring on 50 in all, because they do have a number of vacancies.

The foreign offices, again, none of these are within my chain of command, but they have explained to me they are really working on hiring. They have vacancies as well.

Ms. DEGETTE. And to what do you attribute these vacancies? Is it just the vacancies we've seen throughout the agency since 2016?

Dr. WOODCOCK. There are—the administrative problems are one problem with vacancies. Another problem with vacancies, of course, is the roaring economy and the fact that people can make more money elsewhere.

The Center for Drugs, for example, we have to hire 400 people to net less than a hundred, because we're losing—you know, we're so attractive—our staff is so attractive elsewhere, so—but we do have administrative problems with hiring.

The foreign offices, it's more complicated. People don't necessarily want to move their family overseas to some area in India for many years. And——

Ms. DEGETTE. Dr. Denigan, I see you nodding at that. Would you like to comment on that?

Dr. DENIGAN-MACAULEY. Yes, it is correct. I mean, once they even—through the direct-hire authority, while it's good, it still is

going to take 2 to 3 years for that inspector to be able to get the experience to then be able to go overseas, as Dr. Woodcock had mentioned. And plus, if it takes 2 to 3 years, even if they are ready to go, we found that it can take up to 2 years just to get over to the post. And if you're talking about uprooting families, getting security clearances, medical clearances, finding schools, housing, things like that, you can give up in the process. So it is very challenging.

Ms. DEGETTE. And, Dr. Woodcock, what can we do to try to alleviate some of those challenges and expedite it? Is there something Congress can do to help?

Dr. WOODCOCK. All right. Well, I think there are many things Congress can help us with. In the hiring area, I believe—you know, many of the things that were discussed, for example, a single investigator. Well, if we sent a team, then we do half as many inspections. So we're going to need more investigators if we want to have fuller coverage. All right?

Translation, we are working on that. We do have the funding, and we are working on getting contracts for independent translators per country that, you know, are not related to the firm or any other part of the country.

Unannounced inspections is, again, a tradeoff, because they are very inefficient, because we send people over there and then they aren't operating, and they're in the middle of China and they don't have anything to inspect, for example. So that's—if we had—we agree that they would be useful, but we feel that there's a tradeoff there between actually covering the inventory and then how deeply we can cover the inventory, and that should be obvious. So hiring, very important.

The authorities you gave us under Cures is really helping the Center for Drugs in hiring people quickly that are qualified scientific experts. And so those type of authorities are very helpful.

Ms. DEGETTE. Thank you. Thank you so much. Lot more questions, but good news, we have a lot more Members here.

Mr. Guthrie, I recognize you for 5 minutes.

Mr. GUTHRIE. Thank you very much. And I appreciate it. And we're kind of going down the same path, I think, with our questions.

First for Dr. Denigan, just to establish the difference in on-site—or preannounced and unannounced inspections. So do announced or unannounced inspections better enhance the integrity and effectiveness of an inspection, and how does the FDA use both announced and unannounced?

Dr. DENIGAN-MACAULEY. So, generally, the FDA uses unannounced inspections with their foreign offices. They've said that for logistical reasons they need to give up to 12 weeks' notice for those coming from the United States because of the challenges of just doing the logistics. So that's a real value of the foreign offices because they're there, they have the in-country intel, and they can get there for the unannounced inspections.

Mr. GUTHRIE. Great. Thank you very much.

And it does, Dr. Woodcock, kind of make sense logistically it's easier to do unannounced inspections, easier to send an inspector to Long Island than to interior of China, and I understand the

issues with that. Having said that, how do you weigh the risk of maybe we need to do an unannounced inspection even if you—I know you have to call ahead. How do you weigh the risk of besides? All right, there's one, we're just going to do an unannounced inspection even though we risk of getting there and they're not operating or those types of things?

Dr. WOODCOCK. Yes. We do, for example, for cause. Say, if we have a whistleblower or a complaint, we will go in unannounced, even in a foreign country. So we do unannounced inspections both by foreign offices and domestic. But I will say, I mean, it is just a hypothesis anecdotal that the unannounced inspections are so much better, that it's worth all the costs, all the time. Ninety percent of the data integrity problems that have been found recently have been found by our domestic inspectors going and doing announced inspections. And why is that? Because they're very good. Because our regulations under part 11 require them to have computer systems with audit trails. And either they don't have those, or if they have messed around with them, our people can find it. So they have found a lot of the problem—a lot of the problems have been found by announced inspections.

Mr. GUTHRIE. OK. Before I came here, I was in manufacturing. I was a quality engineer. So do you use independent auditors? Is that permissible with you? Because I know when Ford or GM will do auditor, they'll hire—or the company being audited to sell to them will hire someone to come in that everybody agrees is an independent auditor.

Dr. WOODCOCK. Yes. If companies get into trouble, all right, and they are having trouble meeting the minimum standards, which are GMPs, we would frequently suggest to them that they use independent consultants who audit them. Sometimes they will give us reports on the progress of the firm.

Meanwhile, the firm won't be able to import into the United States because we do have a very strong regulatory tool for foreign manufacturing, which we can do an import alert, and then they can't send anything to the United States while they're remediating their problems. So we do—and when we do consent decrees, it may include reports by external auditors.

Mr. GUTHRIE. OK. Well, thanks. Just kind of specific questions to make sure we get it get on the record. Does the FDA have evaluation criteria for effectiveness of its foreign drug inspection program? If so, what are the criteria? And has FDA conducted any sort of review of the effectiveness of the overall program, and if so, what are the findings?

Dr. WOODCOCK. Well, I think that's a very good question. I believe that we really need to do more of this. Of course, it's hard to assess the counterfactual, what would have happened if we weren't there, right? And so we do need to, as I said in my oral testimony, we really need to work on standardization of the inspection program, standardization internationally, and then we can put in some evaluations about the consequences or the results.

Mr. GUTHRIE. Great, thanks. I want to ask a final question. I know we talked this week about nitrosamine and NDMA found in trace elements that, if anybody hears that you're more at risk of not take—you need to take your blood pressure—you're more at

risk of high blood pressure than any risk from nitrosamine. So I want to establish that before we go forward. But have you—what have you done—what's the reaction of FDA? Are you testing for NDMA during its foreign drug inspections now?

Dr. WOODCOCK. Right. No, that's not really possible. That's a different part of the FDA. I think some folks have a misunderstanding what an inspection can actually do. It can look at what the firm does, all right? It can't really—we don't go and do——

Mr. GUTHRIE. You're not testing—you're inspecting, not testing?

Dr. WOODCOCK. That's correct. So what—we have some of the best drug laboratories in the world, and they have been doing—they establish the test first, the benchmark tests that are being used, and we posted them so everyone could use them. And then we are getting samples. We've tested over 1,500, I think, samples of different drugs for nitrosamines, and we're continuing this testing and getting the manufacturers to do the testing as well.

Mr. GUTHRIE. I'm out of time. I want to emphasize really quick, but if somebody's taking medicine and they think it's in this category, they need to take their medicine?

Dr. WOODCOCK. They need to, and what's on the market now——

Mr. GUTHRIE. I want you to say that.

Dr. WOODCOCK [continuing]. Of the ARBs of the blood pressure medicines is OK. We've recalled the ones that aren't OK.

Mr. GUTHRIE. OK, thank you.

Ms. DEGETTE. I just—I know the witnesses know this, but I just want to let you know that Members are going to be coming back and forth between this hearing and a, unfortunately, coscheduled hearing with the Health Subcommittee.

With that, I'm going to thank Mr. Tonko for staying here and recognize him for 5 minutes.

Mr. TONKO. Thank you, Madam Chair, on both counts.

As we heard from GAO today, one of the big challenges that FDA inspectors face in certain foreign countries is the language barrier. We have heard throughout the years that FDA inspectors are not usually provided with an independent translator. In fact, GAO's testimony notes that FDA generally relies on the firm itself to provide a translator. According to GAO, FDA investigators stated that this practice, and I quote, "can raise questions about the accuracy of information FDA investigators collect," close quote.

So, Dr. Denigan, what type of concerns does the use of nonindependent translators raise?

Dr. DENIGAN-MACAULEY. Yes. The use of a nonindependent translator definitely raises concerns about the accuracy of the information that they're receiving, particularly in those countries such as South Korea, China, Japan, where their native tongue would not necessarily be that language. The investigators that we spoke with said that at times people can provide translation that they don't have the knowledge to be doing the translation. It's simply the only person in the company that can speak English and, therefore, is doing it. So it could be inaccurate that way. It can be misinformation on purpose. So there are a variety of concerns that we would have with not having an independent translator.

Mr. TONKO. Well, this isn't a new issue. So does GAO and the subcommittee, as we go forward, need to look more closely at it, since we raised the same concerns over some 10 years ago?

Dr. Denigan, why has this been such a longstanding problem if it was identified 10 years ago?

Dr. DENIGAN-MACAULEY. I don't know that I have the answer to that. I know that FDA has made significant changes, but they have not made progress in this area of providing translators. The China office, however, has taken initiatives to use their foreign nationals that work for FDA to help with the translations, and at times they have said the company is not interpreting correctly. This is what is really being said.

Mr. TONKO. And, Dr. Woodcock, FDA told committee staff that using translators from the firm puts inspectors at a disadvantage. Are you comfortable with inspectors in a foreign country relying on a translator who works for the company FDA is inspecting?

Dr. WOODCOCK. No. I think it would be better for us to have our own translators, and we are in the process of seeking out contracts so that we can do that.

Mr. TONKO. And as you do that, like, what is involved in the exploring of having more independent translators doing these foreign inspections?

Dr. WOODCOCK. Well, we have to go through the contracting process, which is elaborate, but we can get that done, and there are certainly large number of groups—because there's a great deal of commerce with China and India—there are a large number of independent translating groups that exist that one of which could be contracted in each country to provide this type of service to the FDA inspectors.

Mr. TONKO. And, Dr. Denigan, based on your audit and discussions with FDA inspectors, what are the concerns associated with sending a single inspector to conduct a foreign inspection?

Dr. DENIGAN-MACAULEY. There are a variety of different concerns. One can be safety. For example, on one audit over in China, the auditor was actually whisked away to a room and was held because they didn't believe that they were the auditor. And, until the Chinese counterpart was able to have conversations, she feared for her own safety. And actually, I think in that example—sorry, that was a bad example—there were two there, but even with two, that was of a concern.

The other thing is, these campuses are huge, they're quite large, and it's very difficult to be able to do a complete inspection. And, if you're coming from the United States, then you don't have the flexibility, necessarily. You have to get a certain amount of inspections done in 3 weeks. And so, if you take more time at one spot to be able to do a thorough inspection, then you're taking away from another inspection.

Mr. TONKO. And, Dr. Denigan, it's reported that 80 percent of its foreign drug inspections—the FDA's report, that 80 percent of its foreign drug inspections are performed by solitary inspectors. Do you believe that that number is making a huge impact on the ability to sufficiently inspect these facilities?

Dr. DENIGAN-MACAULEY. I do know that domestic inspections also have solitary inspectors, but they don't have the challenges do-

mestic stateside that they have overseas. And when we go and we visit these plants, I mean, they are in very remote locations and in cultures that are different than our own, and it does raise concerns.

Mr. TONKO. I thank you very much.

And with that, Madam Chair, I yield back.

Ms. DEGETTE. Thank you very much.

I now am pleased to recognize the gentleman from West Virginia for 5 minutes.

Mr. MCKINLEY. Thank you.

I think, Dr. Denigan, you said in your report and in some of the documents that, now that the FDA has opened offices, the GAO has reported that the open offices in China, India, Europe, Latin America, and elsewhere to increase the number of inspections that are taking place, this since 2009. So from an engineering perspective, I want to see from the metrics. Now, so have these increased number of inspectors being on site, have they led to—are we seeing fewer recalls, better productivity? What are we seeing from the result of having the increased inspection?

Dr. DENIGAN-MACAULEY. So that's one of the reasons that GAO has made recommendations over the years, that FDA needs to tie the outcomes of what the foreign offices are doing to results, so that they can better measure their impact. One would think that, with unannounced inspections, that you could tie, for example, looking at the number of warning letters or the number of serious problems that they find.

Mr. MCKINLEY. So are you testifying that it has been—it's been cost effective to do this?

Dr. DENIGAN-MACAULEY. No, I'm not saying that. I'm saying that FDA has not looked at how effective the offices have been.

Mr. MCKINLEY. OK, thank you.

Now, let me go back, again, Dr. Woodcock, here a little bit on—I come from the construction industry. We also have some coal mining in West Virginia. Neither one of those industries, neither one of them get an advance notice when there's an OSHA or MSHA coming into their sites. I can't—I'm still struggling with your idea or your concept of giving advance notice to someone to come in. Can you try that one more time to get it past me? Because I'm not buying this idea of "We're going to let you know," because we know China's gaming the system. Give me a little help.

Dr. WOODCOCK. Certainly. We—as I said, we began as a domestic agency, and domestic inspections are not preannounced. However, when we began inspecting overseas, different countries have visa requirements. The travel is—you know, the location of the site was difficult to ascertain. Now, that's improved over time with various things, and particularly it was difficult to know whether the site would be manufacturing at the time we inspect them. That's very important.

Mr. MCKINLEY. OK. I'm not buying the thing about the visas, because I would assume that so much of it is taking place in China. We have someone or a group of people over there, that they're going to continue to travel the circuit and do their inspection with that.

Dr. WOODCOCK. No. The number of inspectors we have in China and India are not sufficient to perform the number of inspections that are needed. So most of the inspections need to be done by domestically based inspectors who are sent to other countries. And those are the ones——

Mr. MCKINLEY. Can you come to the office? I'd like to follow up on this, because I don't think we have enough time to get into that. But I'm not convinced at all that a preannounced—alerting someone that we're going to come in and look at you is going to get the results we want.

Now, I also—but I want to follow up also with you on the thing that 90 percent of American prescriptions, from what I understand, are generic, but they only amount to about 56 percent of the recall. So I'm curious, either one of two things, either they're doing a good job replicating them or they need more scrutiny. Which is it?

Dr. WOODCOCK. I'm not familiar with the figures you're using on the recalls. Could you explain a little bit more?

Mr. MCKINLEY. Yes. I don't have the source of that, but we have 56 percent of all of the recalls have been generic. If that's not correct, if you don't—and I can't back that up just at this moment—what is that? What would you say is the percent? Is it comparable?

Dr. WOODCOCK. Well, we'd be glad to work with you on this, because I think it's a little more complicated than that. In the first years after a new innovator product is launched, there may be safety recalls and different things that are unrelated to the quality of the product. So first you have to talk about what kind of recalls are you talking about, and then where did you get these statistics, because I'm not really clear on this.

Mr. MCKINLEY. Well, the reason I'm saying that—I only have a few seconds left—is there are some Members of Congress who have been suggesting that generic drugs are not safe. I'm trying to make a determination whether or not they are safe or not based on the fact that if 90 percent of us are generic and only 56 percent are recalled, does that mean they're safe, or what's happening? Are generic drugs safe for people to take?

Dr. WOODCOCK. Yes. We stand behind the generic drugs. I will point out that we do have good safety detection systems, right, and the biggest risk right now we see to the public is from compounding where we have multiple outbreaks that we continue to have of humans beings harmed by compounded drugs.

Mr. MCKINLEY. Thank you.

Dr. WOODCOCK. So we have a system that can detect problems when they occur, and we do not have problems with 90 percent of the drug supply. The generic drug supply is reliable.

Mr. MCKINLEY. My time's expired. So before I get yanked, I'll yield back.

Ms. DEGETTE. I thank the gentleman.

Now I'd like to recognize the gentleman from California, Mr. Ruiz, for 5 minutes.

Mr. RUIZ. Thank you very much.

This issue is becoming more and more important because of the inability of middle-class families to afford their medications, and they're getting medications from other places, as well as legislative ideas to import medications to help lower the cost for people. And

as a doctor, I'm concerned because we know what a placebo pill can do to a diabetic's blood sugars. And when patients think that they're—they need to take a certain drug, they're actually taking a different drug. And then, if it's contaminated, then it may make their illness even worse.

So the FDA faces the enormous challenge of inspecting the thousands of firms around the world producing drugs for the United States. Compounding the challenge is the fact that, over the years, some firms have reportedly engaged in fraudulent behavior to cut corners and deliberately conceal failures from the FDA inspectors.

In the past year, for example, press reports have offered disturbing accounts of such fraud. In January, Bloomberg News reported incidents of, quote, "computer files found deleted and employees caught on a company's own security cameras shredding documents the night before an inspection," unquote.

In May, NBC spoke to a former FDA inspector and reported that, quote, "FDA inspectors struggl[ed] to keep up with foreign drug manufacturers that may bury or hide problems in their production," unquote. In an article in October in Stat News, it was reported that violations of data integrity are persistent and ongoing in overseas drug manufacturing plants.

Madam Chair, I would like to request that these reports be entered into the record.

Ms. DEGETTE. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. RUIZ. Thank you.

Dr. Denigan, when you traveled abroad for your audit work and talked to inspectors in China and India, did you hear stories such as these?

Dr. DENIGAN-MACAULEY. Unfortunately, we did. There were instances where inspectors gave 30 minutes' notice they were on their way, and when they got there, they saw documents, bags of documents being disposed of. And they said, "Don't do it," took photos, ran in to show their credentials. In the time that they got back, in the few minutes it took to show their credentials, they blatantly disregarded them and disposed of them.

Mr. RUIZ. Dr. Woodcock, you were quoted in the previously mentioned Bloomberg News story that there were high profile cases of, quote, "overt and deliberate fraud," unquote, by certain drug companies. Dr. Woodcock, how should we put these reports in perspective? How pervasive do you think this problem is? And what tools does FDA have to sufficiently root out any cheating or data manipulation, if it is occurring?

Dr. WOODCOCK. First of all, I should point out that we see this in the United States or in the North America or the Americas as well as ex-U.S. We have seen cases of—serious cases of data integrity problems.

The second thing I should point out, which gets to——

Mr. RUIZ. So how—so how pervasive is this?

Dr. WOODCOCK. Well, that's what I'd like to show here. Slide 12. If I could show—pull up the slides. No?

Mr. RUIZ. Just tell me if you can, because my—the time is ticking.

Dr. WOODCOCK. About—in the United States, about 93 percent of firms who are inspected pass the inspection, right. In India, 83 percent. So there's a 10 percent difference. That means 83 percent of the firms we inspect fail to be adequate and pass the inspections. They have the lowest percentage. China's percent passed is very close to the United States'.

Mr. RUIZ. Do you—I have about a minute left. Do you feel that unannounced or short-notice inspections could help you better discover manufacturing issues or even data quality issues when they are occurring?

Dr. WOODCOCK. Certainly. Those are desirable. You just have to think about the tradeoffs in doing that. But no one is opposed to those, and we do them routinely for for-cause inspections.

Mr. RUIZ. Recently, the FDA told the committee that firms were inspected every 2½ years, more or less, but given that the reports we have seen about this issue with some firms, including what you yourself have called, quote, "overt and deliberate fraud," are you comfortable inspecting foreign firms as the current model and resources allow?

Dr. WOODCOCK. Well, as I said, 90 percent of this fraud has been detected under the current system in the way——

Mr. RUIZ. So your—so your acceptable level of error is 10 percent. You're trying to tell me that it is OK to have 10 percent error in inspecting the quality and the safety of our medications?

Dr. WOODCOCK. We don't know what the error rate is because it's impossible to show a counterfactual, as I said earlier. We know that we detect fraud fairly routinely when we go in, even on an announced inspection, because we can look at the computer records and——

Mr. RUIZ. So do you think that it's working?

Dr. WOODCOCK. I believe, as I said earlier, that we could use more inspectors. We could do more unannounced inspections. That would be desirable. We could have more team inspections.

Mr. RUIZ. My time is up. Thank you.

Dr. WOODCOCK. Those things would be good.

Mr. RUIZ. Thank you.

Ms. DEGETTE. The Chair now recognizes the gentleman from Virginia for 5 minutes.

Mr. GRIFFITH. Thank you very much.

Always good to have you all here. Thank you so much, particularly Dr. Woodcock, who always does a great job. But I've got some tough questions today.

So, Dr. Woodcock, according to an article in Wired in July of 2017, a drug firm in northeastern China, in essence, took an FDA inspector and her translator hostage during an inspection. Dr. Denigan mentioned this earlier. The FDA employees were finally freed after about an hour when Chinese regulators interceded. And the FDA Deputy Director concluded in an internal email that the firm resorted to appalling intimidation tactics because the inspection was not going well. However, FDA declined to classify the incident as an inspection refusal, which would be grounds for an automatic import ban, because the firm manager wasn't making a specified refusal when he imprisoned the FDA employees.

Why isn't imprisonment of FDA employees classified as a refusal of inspection by the firm? And let me just say so folks back home understand. It was the conference room that Dr. Denigan mentioned earlier. Imprisoned is a legal term of art as I'm using it here. It does not mean they were placed in a dank cell and only allowed to have food and water, bread and water brought in. But it is technically an imprisonment when you refuse to let somebody leave the conference room.

So, you know, how come that wouldn't be grounds for an automatic import ban? It seems like to me it ought to be.

Dr. WOODCOCK. Well, that's a legal question that lawyers would have to sort out, whether it met the context.

Mr. GRIFFITH. And I've never had great respect for the lawyers at FDA after NECC, and they refused to get a search warrant after Ohio and Colorado both told them there were problems, and nobody in the FDA legal office thought that was sufficient to get the probable cause to get a search warrant, which might have saved 53 lives.

That being said, you know, it seems to me it would constitute circumstances, you know, of delaying, denying, or limiting inspection or refusing to permit entry or inspection for purposes of section 501(j)(2), little 2, under the Food and Drug and Cosmetic Act.

And, Dr. Denigan, you mentioned some things earlier that were similar to that—not quite as bad as taking somebody a prisoner—but why aren't we being more forceful with these foreign companies and just saying, "If you don't cooperate, you're out, you won't be selling in the United States"?

Dr. DENIGAN-MACAULEY. Well, actually, as part of our ongoing work, I think the inspectors have raised concerns, and they've put them down as serious deficiencies, and there has been times where those concerns have been downgraded. And we plan to look at that in our ongoing work.

Mr. GRIFFITH. And I appreciate that. You know, I was brainstorming on this last night because, to me, this is extremely important, you know. We're working on bringing down prices of drugs, but making sure the drugs actually do what they're supposed to and are not adulterated, don't have harmful products in them is extremely important.

And you talked about the large campuses and how it's hard for people to cover the large campus. So, as we were brainstorming, and I want to hear from both of you as to why this wouldn't be something we ought to be talking about.

You know, we could get young people right out of undergrad to come in there. They don't need 3 years of training. You may need somebody like that to do the big stuff, but you don't have to be a gourmet chef to go into a French restaurant and determine that the bathroom is not clean.

It would seem to me that, for pennies on the dollar, lots of young people would love the opportunity to travel abroad and go in and help somebody who's got all that 3 years of training, but help somebody figure out, "OK, building A is dirty. I don't know what's going on. You might want to go look at it." It seems to me we could magnify our inspections and our ability to inspect if we did something like that, and I'm happy to work with you on it.

Dr. Denigan, what do you think of that? And, Dr. Woodcock, I'd like your opinion too. I always respect both of you.

Dr. DENIGAN-MACAULEY. Sure. Well, we certainly heard stories of bathrooms that they were using that were covered in feces. They had to go outside to be able to use the facility, raising questions about good manufacturing practices.

Mr. GRIFFITH. And you don't need 3 years of training to be able to see that, do you?

Dr. DENIGAN-MACAULEY. No.

Mr. GRIFFITH. Dr. Woodcock, what do you think? Is this something we ought to be talking about?

Dr. WOODCOCK. Well, it raises the question, Should ORA, the field organization, change its model somewhat? That's what you're proposing.

Mr. GRIFFITH. That is what I'm proposing.

Dr. WOODCOCK. And have more of a sliding scale of capacities, translators——

Mr. GRIFFITH. Right.

Dr. WOODCOCK [continuing]. And so forth. And I think that's worth talking about as far as how—how we cover the entire range of problems.

Mr. GRIFFITH. Because, as we're importing all of these substances, whether they be substances that are used for compounding pharmacies or whether they are actual drugs that go straight to the consumer, it just seems to me, yes, you want to have your top dog, but you also can use folks who can just go in and take a look at the bathroom. And it doesn't take a genius to figure out or somebody with 3 years of specialized training to figure out the bathroom is dirty and there's feces everywhere. Thank you very much.

And my time is up, and I yield back.

Ms. DEGETTE. I thank the gentleman.

The Chair now recognizes the gentlelady from New Hampshire for 5 minutes.

Ms. KUSTER. Thank you, Chairwoman DeGette, for your continued leadership on ensuring the safety and inspection of our drug supply chain. And I want to thank our witnesses for being with us today.

Recently, I heard from a constituent from Nashua, New Hampshire, who was very concerned about his blood pressure medication, which has had several recalls. Despite his concerns, he also acknowledged the balance that must be struck in ensuring the safety of our drugs but also the supply of drugs. And it's certainly true and something some of my colleagues have mentioned here today.

Outside of the high cost of prescription drugs, one of the other most frequent concerns I hear about is drug shortages. This committee helped to lead the way in working with FDA and stakeholders to ensure that the agency has the additional authorities and flexibilities that you need to inform and respond to drug shortages as they occur. But, at the same time, we must ensure that every American has access to safe medication through your quality inspection.

So let me turn to my questions. Dr. Denigan, is it true that staffing in these offices has been a continuous issue since the offices have opened overseas? And if so, why is that? And what is the im-

pact on the foreign inspection program, and if you will, what do you need from us?

Dr. DENIGAN-MACAULEY. Yes. Staffing continues to be a problem, and there were visa problems over in China that have since been resolved so that they've been able to get more staff over there. But, overall in the foreign offices, staffing has been a challenge, and they have critical vacancies of these expert investigators.

Ms. KUSTER. Now, I know Mr. McKinley asked a series of questions. This appears to be a very bipartisan hearing in terms of our concerns about the effectiveness of the foreign offices and how you intend to address those staffing concerns. If you are not satisfied that the FDA has fully evaluated how its foreign offices should be utilized and improved, what is it that you need from us? Is this a resources issue? What—how can we be helpful? I assume that's the point of this whole hearing.

Dr. DENIGAN-MACAULEY. Well, I think what's concerning is that the data of understanding the number of establishments is challenging to get, and you have firms over there that are registering with FDA that don't necessarily have to. Unlike medical devices, there's no charge to register because it looks good, right. You're registered for FDA overseas, and so that creates noise in the database. And if you don't know the universe of those that you need to be inspecting, I think it's very hard to be able to come up with a strategic workforce plan to know the number of folks that you need to be able to carry out the inspections.

Ms. KUSTER. So couldn't we do something about that? If we're giving them permission to send this medication into our country for sale, somebody's making a profit. Can't we link that more clearly to where has this been made and be much more specific about this? I mean, they have an incentive to want to bring this medication in.

Dr. DENIGAN-MACAULEY. Right. I think that that's what FDA wants to do is to be more strategic about their workforce planning and more risk-based, which GAO appreciates, but they should put their limited resources at the places with the highest risk.

Ms. KUSTER. Dr. Woodcock, do you want to respond? I mean, do you need legislative authority to make this a much more direct link? Why don't we just say, "If you want to send medication into our country, you need to tell us precisely where it's being made, and we're going to come out and look at it."

Dr. WOODCOCK. All right. They usually have to do that now, all right, for application products. So if you send in an application for a generic drug or an innovator drug, you have to tell us where it's going to be made. And we do preapproval inspections before we even let that product on the market.

Ms. KUSTER. So, presumably, you know where they're being manufactured?

Dr. WOODCOCK. Well, not only do we know where, we go there, unless we've been there recently. However, for—there's some loopholes for compounding and for over-the-counter monograph drugs that don't have applications. That's a very large segment, and that's many of the never being—been inspected that were——

Ms. KUSTER. Do you need us to close those loopholes?

Dr. WOODCOCK. It would be—I think we would be interested to work with you on the issue that they can ship to the United States

without ever being inspected right now, because all they have to do is register.

Ms. KUSTER. Right.

Dr. WOODCOCK. And there are other data points, as I alluded to in my verbal testimony, that would be very useful for us to receive as data. For example, we don't know the volume. We know—you said maybe 20 percent of APIs made in the United States, but it may only be an infinitesimal fraction of the actual volume, because we only know the facilities, not how much they're making. And they tell us——

Ms. KUSTER. Well, I hope you—my time is up, but I hope you will work with our committee to tighten this up, because these loopholes sound dangerous to the American people. Thank you.

Dr. WOODCOCK. We would be delighted. Thank you.

Ms. DEGETTE. The gentlelady from Indiana is recognized for 5 minutes.

Mrs. BROOKS. Thank you, Madam Chairwoman. And thank you both for being here and for focusing on this critically important subject.

I want to stay focused a little bit on the staffing issues. And I'm curious, Dr. Woodcock, has the FDA ever used outside consultants to study this in-depth problem rather than GAO—you know, and I appreciate GAO's recommendations and ideas, but this is very complex. Have you used outside consultants, and what have been the results?

Dr. WOODCOCK. We used outside consultants to look at the administrative hiring problems we had, and we even had a public meeting on that that went over all the different problems. The direct hire should help some of that.

As far as an outside consultant to think about the workforce in ORA and how it's deployed, and actually, the people in the foreign offices actually report to a different component, a third component of FDA that's not the Center for Drugs and not ORA. And so I don't know whether they've done a study or not, but we can get back to you on that, and it is a good idea.

Mrs. BROOKS. Were there recommendations that were made that have not been implemented, if you know, and if not, why not? Were they not given, you know, sufficient credit in the recommendations?

Dr. WOODCOCK. I believe in the recommendations that were made on our administrative problems, there's been a stupendous effort to try and turn this ship around and to get the hiring process to something that can actually bring people on board in a timely manner. And as I said earlier, Cures helps us for positions that are Cures eligible.

So yes, we have acted on those recommendations, but the hiring was so problematic, it's going to take us a long time to recover from that.

Mrs. BROOKS. It seems, even if you were able to hire enough people, one of the things you said that I'm very concerned about is the lack of—unless I didn't write this down properly—standardized inspections, and this is an example.

Earlier this year, the committee sent FDA a bipartisan letter asking about the FDA's India pilot program and why the program wasn't extended. In response, FDA told the committee that the

drug inspection initiative was not extended, quote, "based on lack of protocols and evaluation criteria. No formal report or evaluation was completed."

How is this possible? How is it possible that we've got pilot programs with no evaluation, no protocols, no standardized inspections? I mean, who would want to come work for you if you're—if there's no roadmap and there's no standardization of what their work product's supposed to be?

Dr. WOODCOCK. Well, there are two separate issues. There is standardization that ORA has for what its inspectors do and how they document it, and that is written down. And we are working on what we call the new inspection protocol program, which is changing to a more modern, more standardized inspection process and protocol. We've already completed that for sterile products, but we have to go through all the different kind of products.

Mrs. BROOKS. Do you need more people, Dr. Woodcock, to help get this process? I mean, you've just mentioned sterile products. I can't even imagine how many other products. Do you need more people to be focusing on protocols and the standardization of inspections?

Dr. WOODCOCK. If we had more people with doing analysis, as you've pointed out, doing analysis and actually working on these projects rather than, you know, doing the work—the day-to-day work of trying to inspect all these firms, of course, that would be very helpful.

And I will add, there's another component of this since we did the Mutual Reliance Agreement with the EU and all those countries, OK. They do their reports in all different languages, naturally. And so all of us would benefit from a very standardized report document that we could all read without having to translate it into different languages.

Mrs. BROOKS. I was actually going to ask you about the EU reliance. Can you please talk with us about what that means and how long will it take us to realize the benefits from the Mutual Reliance Agreements with the EU? And who else should we—and what does it mean? Can you go into a little more detail on that?

Dr. WOODCOCK. First of all, what it is, is we've agreed with all the EU countries that their inspectors are qualified to inspect the plants within their country boundaries, because each country has different inspectors, right, and that we will accept the results of those inspections, and they'll—they'll send them. And then they don't have to come over to the U.S. and inspect facilities that are here, because they accept the results of our inspections. It doesn't extend to their inspections in other countries, but it does free us up to go send more people to India and China.

Now, that trend has been abrogated, as people pointed out, by the loss of staff in ORA, the loss of people in the inspectorate in the foreign offices, and so we haven't had the capacity, and our number of foreign inspections has actually gone down because of capacity problems, even with the MRA in operation.

Mrs. BROOKS. Well, I certainly hope our Mutual Reliance Agreements can extend, and maybe we can look at other countries as well. Thank you.

I yield back.

Ms. DEGETTE. Doctor, would it be possible to get a copy of that independent report you're telling Congresswoman Brooks about?

Dr. WOODCOCK. Absolutely. We can get that back to you.

Ms. DEGETTE. I think that'd be really helpful. Thank you.

The Chair now recognizes the gentlelady from Florida for 5 minutes.

Ms. CASTOR. Thank you, Chairwoman DeGette. Thank you both for being here today.

I know we've focused a bit on the challenges in staffing, and I'd like to focus a little bit more on the quality of FDA's data. FDA's foreign drug inspection program relies upon having quality data that allows FDA to know which firms to inspect and to review those firms' inspection history. However, GAO has long identified problems with the data FDA relies on for its drug inspection program. In testimony today, GAO states, quote, "data challenges we identified in our 2008 report continue to make it difficult for FDA to accurately identify establishments subject to inspection."

Beyond staffing, Dr. Denigan, what are your main concerns with the way FDA is collecting and using data related to its foreign inspection program? How do these data collection concerns impact the effectiveness of the foreign inspection program?

Dr. DENIGAN-MACAULEY. Yes. So as I mentioned before, the establishments—they have establishments in there that are registering that don't need to, and that creates the extra noise. And, while it's true that 40 percent of those establishments didn't need an inspection, and therefore, FDA was able to say that they went through their backlog, it still creates an inefficiency. They have to take the time to clear out to find out which one of those didn't.

And so the foreign offices can add value. For example, like over in China where they're actually matching up to see does that establishment really still exist. Because, as Dr. Woodcock said, they do change. They go in and out, so it's a snapshot in time. And further, their active pharmaceutical ingredient could be produced in China, for example, and if they ship it to Germany, then it's not subject to an inspection. I know that FDA is very clear of that loophole.

Ms. CASTOR. OK. Let's talk about those two. And FDA told committee staff that some firms on its foreign drug facility list were, quote, "washouts." Is that what you were referring to?

Dr. DENIGAN-MACAULEY. Correct. Those are the washouts that didn't need to be inspected but were on their list.

Ms. CASTOR. OK. Meaning that these firms were not actually subject to inspection for various reasons, including because they were no longer exporting to the United States.

Dr. Denigan, what is the difference—what is the significance of these washouts previously included in FDA's data? Do you have—you said you had concerns about it. I guess this is a really good question for Dr. Woodcock.

Dr. WOODCOCK. Yes. Well, you know, we have various thoughts about this. It's easy for people to register. You just can register, and then you have a sort of branding. You can say, "I'm registered in the United States," and you never have to ship anything to the U.S. And so we have to go to the trouble, as Dr. Denigan was saying, of figuring out where that firm is, figuring out is it shipping

anything into the U.S., what's its status, and then crossing it off the list.

It's possible that some small barrier like a modest fee or something might help with that. I don't know where—how we could do that, but it is possible right now for a lot of firms every year to register with the U.S. and actually not be shipping drugs into the U.S. But it's also possible for them to register and then ship without being inspected if they are one of these loophole firms.

Ms. CASTOR. And then you also raise the problem with facilities. You don't—FDA does not have a firm handle on the volumes being shipped out. Why is that the case, and what are you doing to address that?

Dr. WOODCOCK. Well, we're thinking of doing a regulation, which would be a very long process. The companies have to tell us in what's called right now the annual report. Remember, many of these regulations are very old. But my understanding, at least—I recognize I'm under oath, and I don't have total grasp of the details—but they have to tell us that kind of stuff for the past year. And then they—eventually, they submit that annual report at some time in the next year. So it's a really lagging indicator. And it isn't data, it's in a PDF of a document that they send us.

And what would help, if you all wanted to know the volume being shipped in the United States, we would need something like quarterly data reporting as data in a database rather than—you know, a fillable form rather than sending us a PDF a year later about the volume that was shipped. If we had that type of data, then we could really put together a more complete picture of what's coming into the United States.

Ms. CASTOR. And you need legislative authority to move towards a quarterly data report?

Dr. WOODCOCK. We think we could do that under regulation, but it might take us 7 years.

Ms. CASTOR. Why 7 years?

Dr. WOODCOCK. Because it takes a very long time to do regulations. I know I'm under oath.

Ms. CASTOR. Yes.

Dr. WOODCOCK. I can't say—you know, I can't predict. We could say maybe never, right, or maybe we could do it a little faster, I don't know, but it takes a long time to write, propose, get comments on——

Ms. CASTOR. Gotcha. Yes. We, you know, understand.

Dr. WOODCOCK. I'm sorry.

Ms. CASTOR. Thank you very much. Thanks for making that recommendation.

Ms. DEGETTE. The Chair now recognizes the gentleman from Oklahoma for 5 minutes.

Mr. MULLIN. Madam Chair, you forgot to say your good friend from Oklahoma.

Ms. DEGETTE. My best friend.

Mr. MULLIN. Best friend. There you go. Thank you. Thank you.

Dr. Woodcock, thank you again for being here. I sure appreciate your demeanor and your ability to answer the questions the best you can.

I've got just a few questions I'm going to go through here. How many drug inspections can the FDA conduct per year in India and China? Currently.

Dr. WOODCOCK. Currently. We do have a slide on this. Does anybody know what number that is?

Mr. MULLIN. Everybody likes slides and PowerPoints, don't we?

Dr. WOODCOCK. Yes. Sorry. It's slide No. 4. So if we can get——

Mr. MULLIN. We don't have to get it up. We can just—you can just tell me.

Dr. WOODCOCK. OK. So in—well, this doesn't——

Mr. MULLIN. While they're looking for it—let's let them look for it. I'll go on to another question.

Dr. WOODCOCK. OK.

Mr. MULLIN. How many would you like to be able to inspect in China and India?

Dr. WOODCOCK. Well, if you don't mind me pushing back on you a little bit.

Mr. MULLIN. Sure.

Dr. WOODCOCK. What I would really like to have is a predictive risk model that tells us based on a lot of data who we should really go to next, who's the highest risk.

Mr. MULLIN. Well, the last time you were here, we brought up corruption in China and asked if that could bring up issues. When you start thinking that 45 percent of all of the ingredients in our drugs today made inside the United States come from India and China, huge concern for all of us. And—and so when you start talking about risk data, you can't get the risk—you can't understand what it is you're looking for unless you put your hands on it. I tell all my foremen and superintendents that used to work for our companies when I ran them that, you know, the best way to get the information is to be in the field.

So, once again, how many would you like to be able to inspect? If you could have your druthers and you could—staffing wasn't an issue, what's our current level at now, and where do you think we should be?

Dr. WOODCOCK. Well, it looks like we inspect about—in China? Foreign, we inspect about under a thousand, 966. In China, it looks like maybe about 400. I think it would be higher. I think there would be more unannounced, as was said. There would be more team inspections. I mean, those things all would be desirable.

Mr. MULLIN. So when you go inspect these other 40, what percentage of violations do you find in these facilities?

Dr. WOODCOCK. Well, in the previous slide I showed, 83 percent of China—India passes, 90 percent of China passes, and 93 percent of the U.S. passes.

Mr. MULLIN. Do you think that the 90 percent in China and the 80—what did you say?

Dr. WOODCOCK. 3.

Mr. MULLIN. 83 percent in India is actually accurate, or do you think the—that's not an accurate number because they're changing things before you walk in the door?

Dr. WOODCOCK. I believe there's always some—an inspection is only a snapshot in time. They don't inspect every single system——

Mr. MULLIN. Sure.

Dr. WOODCOCK [continuing]. In the facility. We have lots of cases where we had inspections that were OK, OK, and then all of a sudden, everything was wrong.

Mr. MULLIN. So do you believe it's easier for FDA to inspect our drug manufacturers inside the United States or in India or China?

Dr. WOODCOCK. It's obviously easier to inspect in the U.S., and there's a long history. Back in the nineties——

Mr. MULLIN. Sure.

Dr. WOODCOCK [continuing]. There were many problems and many consent decrees and things, but the intensity of the oversight brought the level of performance up in the U.S.

Mr. MULLIN. So what's the biggest barrier? Why do we have 45 percent of our drug ingredients made in China and India and not here in the United States, if that's where the drugs are coming to anyways?

Dr. WOODCOCK. The reasons that we discussed at the previous hearing are cost of personnel, the lax environmental regulations, which are very—it's a very important issue in other countries compared to the U.S., and, you know, the cost of doing business is lower.

Mr. MULLIN. So we've basically regulated these manufacturers out of the country?

Dr. WOODCOCK. Yes. Well, we feel that advance manufacturing, which is what FDA has been trying to bring about in this pharmaceutical sector for the last 20 years, would—you could bring manufacturing back to the United States, because it's not—it doesn't have a huge environmental impact. It has a smaller footprint, and it's very cost effective, but there is a cost of doing that.

And Sanofi has built a plant in Framingham that they recently announced has successfully completed all its test runs and is one of these plants of the future in the United States.

Mr. MULLIN. We'd love to work with you moving forward on that because we'd love to see the manufacturing come back, and so anything our office can partner with the FDA on, consider us a friend.

Dr. WOODCOCK. We would be happy, because we're very excited about this.

Mr. MULLIN. Thank you. I yield back.

Ms. DEGETTE. The gentlelady from New York is now recognized for 5 minutes.

Ms. CLARKE. Thank you, Madam Chairwoman, and I thank our Ranking Member Guthrie, for convening this timely oversight hearing on the Food and Drug Administration's inspection program for foreign drugs. I'd like to thank you both as well, our witnesses, for being here today to testify on behalf of the FDA and the GAO.

The fact is that our drug supply is becoming increasingly global. Many of the drugs that Americans rely on every day are produced around the world. As such, FDA must adapt to this new reality to ensure that our drug supply remains safe and that the manufacturers are held accountable.

So let me start with you, Mrs.—Dr. Denigan. Why should we be concerned that FDA's inspections of foreign manufacturers might not be equivalent to its inspections of domestic manufacturers?

Dr. DENIGAN-MACAULEY. Well, that equivalency is important. They don't announce inspections here for a reason, and so you

want—for the same reason, you want to see—I know it's a snapshot, but that's your best chance of being able to see what the process actually looks like, not what it looks like after 3 months of working with a contractor, for example, to get into compliance.

Ms. CLARKE. One of the committee's longstanding concerns is FDA's ability to get out and inspect the thousands of firms around the world. After Congress gave FDA more authority and resources, FDA was able to conduct more inspections. However, after 2016, the number of inspections went back down.

Dr. Denigan, why did the number of FDA's foreign inspections decrease in recent years, and what does this mean for the FDA's ability to oversee the Nation's drug supply?

Dr. DENIGAN-MACAULEY. Well, I think, as Dr. Woodcock has pointed out, the staffing shortages have been a tremendous strain and have made it very challenging to conduct. In addition, we do have concerns about the accuracy of the data to understand the denominator of those that they need to inspect.

Ms. CLARKE. Very well.

Dr. Woodcock, FDA has made improvements over the last decade in its ability to inspect more foreign firms, and we are appreciative of that work. But, as we just heard, there's more work to be done on hiring inspectors and getting better data.

Dr. Woodcock, what is FDA doing about all the remaining unresolved issues that GAO has identified in its recent work? And we've been talking about these same issues for two decades now.

Dr. WOODCOCK. Well, we have brought about a lot of change. We're doing more foreign inspections now than we're doing domestic inspections. We are working on hiring. The FDA has just received direct hiring authority for the field inspectors, and so they have 20 that they're onboarding. They expect to hire a total of 50 by the end of this upcoming calendar year. So that would be an addition in the pharmaceutical inspectorate.

We've done what we can on data, and we're very interested in working with the Congress on better data sources so that we can have a better understanding of the firms that are shipping drugs into the United States.

As far as cleaning up the registration database, there are a variety of techniques we could use to do that. I mentioned one, perhaps a modest fee for listing might discourage some of these foreign entrepreneurs from listing with never having an intent to ship into the United States, but there might be other ways to do this, and we could talk about that.

And then, you know, better data that we could make a true predictive model instead of our site selection model that we have, but a true predictive model based on data would be a tremendous advance.

We also are working on advance manufacturing, which could actually bring manufacturing back into the United States, or if it were outside the U.S., it would be much better controlled. We would know even remotely with that kind of manufacturing if things were going wrong.

Ms. CLARKE. Well, Dr. Woodcock, that sounds promising. I'd like to encourage us to really move in that direction, because our reliance on foreign manufacturing, I believe, is only likely to increase

as we look at the sort of aging of Americans, the boomer generation and the young folks coming up who, you know, unfortunately, may need some pharmaceuticals to make sure that their quality of life is preserved.

So, Dr. Denigan, overall, do you believe the FDA is where it needs to be to effectively regulate the drugs coming from overseas, and if not, what more does the FDA still need to do?

Dr. DENIGAN-MACAULEY. Well, they certainly have made great strides since 1998, and I know I'm going to run out of time. But clearly, they need to work on getting folks on board, keeping them on board, perhaps looking at other models. You know, the Foreign Service, they're now a global agency, and they weren't designed to be a global agency originally.

Ms. CLARKE. Very well.

Thank you, Madam Chair. I yield back.

Ms. DEGETTE. Thank you very much.

The Chair now recognizes Mr. Walden for 5 minutes.

Mr. WALDEN. Thank you very much, Madam Chair, and again, thanks for having this really important hearing. To our witnesses, thank you both for being here.

Dr. Woodcock, FDA in January of 2014, the FDA began a pilot program in India of no-notice and short-notice inspections of drug manufacturing plants instead of customary preannounced inspections. And over the course of 18 months, I'm told, the unannounced inspections revealed some troubling conditions, from a bird infestation at one plant to a plant that entirely faked its environmental monitoring data, purporting to have screened for microbile and contamination when it had not.

Under the India pilot program, the rate at which FDA inspectors recommended the most serious findings of official action indicated an increase by almost 60 percent. Yet in July of 2015, the FDA discontinued the program and resumed preannounced inspections.

So, considering the high rate at which inspectors found serious violations, why did FDA discount—or discontinue, I'm sorry—this program?

Dr. WOODCOCK. Well, this program was done by the India office, is my understanding, OK, which reports through a different structure. And apparently, it was simply—it wasn't really a program, it was an initiative of the India office, and they decided to conclude it after a certain amount of time. And so——

Mr. WALDEN. Do you have any idea why, though?

Dr. WOODCOCK. No.

Mr. WALDEN. Because it would seem to identify a better path forward if you're trying to uncover problems at these facilities.

Dr. WOODCOCK. Well, there were resources involved. The India office and other personnel had to do a lot of additional work to arrange this travel and enable the inspectors to kind of show up in a surprise. The foreign offices currently do unannounced inspections when they have inspectors resident in the foreign offices. They do unannounced inspections.

Mr. WALDEN. Do we have them in India and China?

Dr. WOODCOCK. Yes. We do have inspectors there.

Mr. WALDEN. But do they do unannounced inspections?

Dr. WOODCOCK. Yes, they can do unannounced inspections.

Mr. WALDEN. And do they?

Dr. WOODCOCK. Yes, uh-huh.

Mr. WALDEN. Yes.

Dr. WOODCOCK. It's the domestic people who travel over and make these long trips where they're, for 3 weeks, they're going to inspect three different silos. They want to make sure they're operating and so forth that are the preannounced.

Mr. WALDEN. So, rather than discontinue due to—I've been told it was also a lack of protocols and criteria that may have led to this discontinuation. Do you think they should have developed evaluation criteria or undertaken a formal review of the program?

Dr. WOODCOCK. Well, again, I don't know enough about it.

Mr. WALDEN. OK.

Dr. WOODCOCK. It's not in my chain of, you know, responsibilities. Certainly, we're being urged today to evaluate—to develop and evaluate such a pilot.

Mr. WALDEN. Which is—and I'm sure you—you know that it raises issues for us. I mean, we look at that and go, wow, something—they were uncovering more when they did that type of inspection.

Dr. WOODCOCK. Well, that isn't clear. And, with all due respect to my GAO colleague, all these ideas are anecdotal. We know that 90 percent of the fraud and so forth that we uncover in our inspections is by—in foreign countries is by domestic-based inspectors who go over there and do unannounced inspections, and they still find this fraud and so forth. And a tremendous amount has changed over this period, even from 2014, but nobody is denying that unannounced inspections, team inspections, more inspections in the foreign area wouldn't be a good idea.

Mr. WALDEN. Dr. Denigan, do you want to comment on any of this?

Dr. DENIGAN-MACAULEY. Sure. Based on the data that we have, the whole value of the foreign offices is to provide—not the whole value, but one of the major contributions of the foreign office is to be able to get local intel. And, based on the local intel that the India office found, they had lapses in integrity of quality, production, laboratory data, significant GMP deficiencies, and firms were found to have been creating records. And so, with their initiative, they did 16 unannounced inspections. And of those 16, 15 of the firms ended up with serious problems. Now, mind you, they targeted firms that they knew were high risk——

Mr. WALDEN. OK.

Dr. DENIGAN-MACAULEY [continuing]. But that's the value of using your resources.

Mr. WALDEN. Yes. Dr. Woodcock?

Dr. WOODCOCK. So some of this is still going on, because part of this program was to develop this intensive intel and brief the inspector about all this before they go in. Now, the Office of Surveillance that we formed in Office of Pharmaceutical Quality with our reorganization, now provides site dossiers for inspectors before they go into a site, and that pulls together all sorts of information. It's probably not as good as the local intel, but we try to get the foreign offices to add that. But that's my point, you know, you're comparing a little bit apples and oranges.

Mr. WALDEN. Right.

Dr. WOODCOCK. I mean, we do all the for-cause inspections we do if we got intel, and we were going to go because of a whistleblower, we would do unannounced.

Mr. WALDEN. All right. My time has expired. Thank you, Madam Chair, and thanks to both of you.

Dr. WOODCOCK. Thank you so much.

Mr. WALDEN. We all want to get this right and make sure we have a safe supply chain, so thank you.

Ms. DEGETTE. The Chair now recognizes the gentlelady from Illinois for 5 minutes.

Ms. SCHAKOWSKY. Thank you so much, Madam Chairman.

There's so much going on today, and so I was in all kinds of other places, and I missed your opening statements, and I apologize for that. So I'm trying to figure out what to worry about or not to worry about. And, for example, I received a—where did it go?—a letter. Oh, OK. There it is.

I received a letter from a constituent, Chris Collins is his name, in September. And he wrote to me about his belief that, quote, "offshoring of generic drugs has made the United States exposed to potentially unsafe and ineffective medicines and deprives us of a domestic supply of critical medicines in case of a national emergency." And then he quotes from a book, which may be totally a scam, I don't know, "A Bottle of Lies," that suggests in a quote that generic—quote, "generic drugs are poisoning us."

So there are two issues here. One is offshore, that so much of our supply is coming from overseas. What it says in our memo is that FDA estimates that nearly 40 percent of finished drugs, drug products, and 72 percent of active ingredients come from overseas. So I'm trying to divide out——

He's also—he's complaining about generics and he's also complaining about overseas. So first of all, is there a difference in imports? We import brand name as well as generics? Is that the case, Dr. Woodcock?

Dr. WOODCOCK. Yes. Those figures include both.

Ms. SCHAKOWSKY. And is it about even number of generics, brand names, or——

Dr. WOODCOCK. That I could get you.

Ms. SCHAKOWSKY. OK.

Dr. WOODCOCK. We have all these figures cut many different ways. But, certainly, a large number of brand names source their API from India or China or elsewhere. And forever, a lot of brand names have been made in Europe.

Ms. SCHAKOWSKY. So I'm trying to understand, Dr. Denigan. So, from the GAO, what am I to be worried about? What is the problem?

Dr. DENIGAN-MACAULEY. Well, it's true that the majority of our drugs, whether it's generic, over-the-counter, or brand name, are coming from overseas. And I think the concern is ensuring that the current tools that FDA has at its disposal are being used to their maximum. It would be great if we could move towards advanced manufacturing and be able to enhance our capacity here, but the fact of the matter is these are the tools that they currently have, and they need to staff up these offices, and they need to ensure

that the inspections are as equivalent as possible to here in the U.S.

Ms. SCHAKOWSKY. So it's something about minimum standards. I'm looking for the language. It says the Current Good Manufacturing Practices regulation, CGMP regulation, lay out minimum requirements for the methods, facilities, et cetera. Is that what we want? What is—minimum doesn't feel good to me.

Dr. WOODCOCK. Well, I just spoke to a large group of manufacturers yesterday, many of them from brand name, and they agree. All of them aim at this minimum. That's one of the problems. That quote, I believe, or something like it, comes from a report on shortages which points out that having true reliability of a supply requires quality maturity. GMPs make sure that, if you make a product, it'll be fit for purpose that day. It doesn't say that 6 months later, you're going to be able to keep making the product at the same level.

So we feel that we would like to have a positive program as well where we recognize excellence wherever it occurs so we can incentivize manufacturers and purchasers to recognize quality, high quality.

Ms. SCHAKOWSKY. Is part of the problem, Dr. Denigan, we have to staff up, there has to be more resources to do the number of inspections that would make a difference?

Dr. DENIGAN-MACAULEY. Well, I'd be concerned at just staffing up, because there's concerns on being able to not only through the direct-hire authority to get them on board, but to keep them on board. And there are problems that, indeed, they go over on 2-year rotations in the overseas offices, and they come home, and they don't have a good way of integrating them back like they do with other offices that are more familiar with how to do that.

Ms. SCHAKOWSKY. Thank you. I appreciate this.

I yield back.

Ms. DEGETTE. The Chair now recognizes the chairman of the full committee, Mr. Pallone, for 5 minutes.

Mr. PALLONE. Thank you, Chairwoman DeGette.

As has been mentioned today, this committee has been examining FDA's foreign drug inspection program for nearly two decades. And, without question, the FDA has made progress thanks in part to new legislation. But I mentioned in my opening statement, over the years, Congress has taken various steps to improve FDA's ability to conduct foreign inspections. But despite this, FDA's foreign drug inspection program continues to be challenged by the same longstanding issues that have persisted for years.

For example, as we heard from the GAO today, staffing continues to be a constant challenge for FDA's foreign drug inspection program. To assist, Congress reauthorized GDUFA, which allowed FDA to collect generic drug user fees, which could then be used to hire additional inspectors.

So, Dr. Woodcock, the 2016 GAO report found that only 8 percent of GDUFA inspectors were actually doing foreign inspections. How has FDA used the GDUFA resource to increase its foreign inspection capacity, if you will?

Dr. WOODCOCK. Well, the field has—the field organization, ORA, has gotten what they call a cadre or group of people who strictly

do foreign inspections, and then they qualify the other investigators to also be able to do foreign inspections. So the goal is to probably increase the number of people who do primarily foreign inspections. But we're challenged by the fact the entire field force is way under capacity, and they need to hire up.

Mr. PALLONE. OK. We focused on FDA's role with these drug products overseas, but we know that domestic importers also play a role, and these companies have a responsibility to conduct due diligence to know where they're getting their drug products from and what kind of quality controls are used before the drugs arrive here.

So, again, what role do U.S. companies play in ensuring that the drug products they import are manufactured in accordance with the quality standards?

Dr. WOODCOCK. Companies are required as part of good manufacturing practices to validate their suppliers, to test incoming APIs or excipients or other ingredients that they'll put into their product if they're making them in the United States to make sure they are fit for purpose. And that same is true if, say, the finished dosage form is in Europe or in India or wherever it is. There are requirements that you qualify your raw ingredients and your suppliers to make sure that they are the quality needed. So that's a requirement that has been in place for a long time.

Mr. PALLONE. But, in the FDA's Safety and Innovation Act, Congress required that the commercial importers register with the FDA, as you said, and that the agency should work with Customs and Border Protection to issue regulations to establish good importer practices for drugs. But can you provide the committee with an update on this work? And what more do you think domestic firms, especially those sourcing raw ingredients from abroad, should be doing to ensure that the products are safe?

Dr. WOODCOCK. Well, the Custom and Border Patrol, that is within—under—the work with them is under ORA. I know significant progress has been made, but I can't give you the details. We can get back to you on that.

The API manufacturers and finished dosage form manufacturers are supposed to qualify all the ingredients that they may use and do tests that are applicable, safety tests or quality tests, to make sure they're using the proper ingredients, and that's their responsibility wherever they're located.

The importers, it's more a matter of the data to make sure we're getting the correct information about what's coming across our border. Now, the agents are right at the border to make sure that we are notified if an ingredient crosses the border or a drug or whatever.

Mr. PALLONE. All right. Let me just add one more thing. The retail chains, they have a different role, as illustrated by the case of Dollar Tree. In that case, FDA conducted inspections of multiple foreign drug manufacturers and found significant violations, such as not testing raw materials and falsifying test results. So in addition to taking action against those firms, FDA also issued a warning letter to Dollar Tree, and they stated, quote, "you're responsible for ensuring that the drugs you distribute are manufactured in compliance with all relevant CGMP requirements for drugs."

So how are retail chains informed of unsafe products in its supply chain? And what more can they do to ensure the safety of the products that they offer for sale?

Dr. WOODCOCK. Right. Well, it depends on what role they have. If they are a distributor, they have a certain role under the GMPs. If they repack and relabel, then they have another level. We can get back to you on the details of what requirements are for every stage in that distribution chain, but they do have requirements.

And you're pointing out one of the loopholes I talked about earlier, that OTC drug manufacturers can register and then ship without having an inspection. And so that's something that allows this type of thing to go on.

Mr. PALLONE. All right. Thank you. And I know through the chairwoman, if you could get back to us in those cases where you said you would, I'd appreciate it. Thank you.

Dr. WOODCOCK. We certainly will.

Ms. DEGETTE. The gentleman yields back.

I really want to thank both of our witnesses for participating today. These are obviously important issues that the committee remains interested in.

And I want to remind Members that, pursuant to the committee rules, they have 10 days to submit additional questions for the record to be answered by the witnesses, and I ask that the witnesses would agree to respond promptly to any such questions.

With that, the subcommittee is adjourned.

[Whereupon, at 11:52 a.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Bloomberg

Culture of 'Bending Rules' in India Challenges U.S. Drug Agency

The FDA confronts creative improvisation in the world's largest generic-drug exporter.

Illustration: Joseph P. Kelly

By Ari Alstedter and Anna Edney
January 31, 2019, 12:01 AM EST

Perched on the edge of a sheer rocky outcropping, Mylan NV's flagship pharmaceutical factory looms over a patchwork of farmers' fields like one of the medieval hill forts that dot the landscape in this part of India.

Mylan is the world's second-largest manufacturer of generic drugs, and though it's run from Canonsburg, Pennsylvania, its operations three hours inland from Mumbai exemplify the central role India has come to play in the global generic-drug industry. About half of Mylan's workforce is based in India. The company's president rose through the ranks of its Indian unit. And that hulking, green, glass-and-concrete complex mounted on the hill is one of Mylan's largest factories.

One of the drugs made in that plant is destined for the U.S., where it's the second-best-selling generic version of Lipitor, taken by millions of Americans to control cholesterol and lower their risk of heart attack. But a review of thousands of reports submitted to the U.S. Food and Drug Administration shows

Mylan's version of Lipitor is more likely to be associated with negative side effects than its rivals: 60 percent more than the top-selling generic version made by a Canadian company and quadruple that of the third-best-selling generic made by an India-based company, according to the reports from doctors, patients and pharmacists.

The so-called adverse events listed in the documents, obtained through a public-information request, include diarrhea and muscle spasms. For some users, the drug didn't work at all. And one report about an 82-year-old patient listed the adverse event as death.

The FDA didn't comment specifically on the reports but cautioned that they don't all indicate a causal relationship to the drug. "Looking only at the number of AE reports for a particular drug does not give a complete picture of its risk profile, compared to other drugs," said Sarah Peddicord, a spokeswoman for the FDA.

A yearlong investigation by Bloomberg News into the generic-drug industry shows FDA inspections at factories from West Virginia to China have found reason to doubt the data meant to prove that drugs made there are safe and effective. The Mylan plant in India is just one of the places inspectors say they've uncovered such alleged problems. But the persistence of these doubts around the world hasn't slowed the FDA's push to bring a record number of new generics to pharmacy shelves in America, as it tries to deliver on President Donald Trump's promise of lower drug prices.

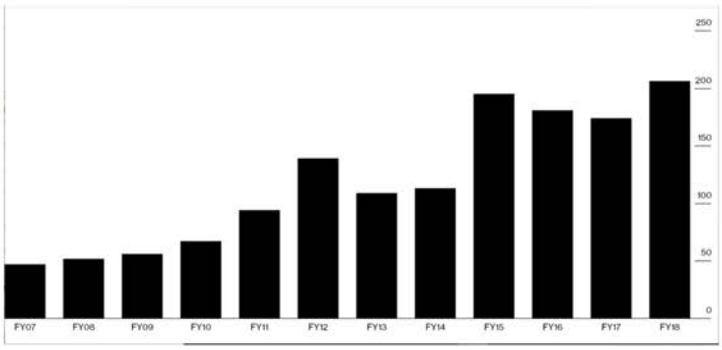
A Mylan factory sits in a Maharashtra Industrial Development Corp. area in Nashik, Maharashtra, India. Photographer: Dhiraj Singh/Bloomberg

India is the world's largest exporter of generic drugs, making almost 40 percent of all new generics the FDA approved in 2018 through October. The FDA has found cause for alarm over the years at Indian factories across companies and around the country, from open toilet drains found at a sterile facility owned by Mumbai-based Wockhardt Ltd. to malfunctioning equipment at one of Dr. Reddy's Laboratories' plants in south India. Since then, a Dr. Reddy's spokesperson said, the company has strengthened "laboratory practices and procedures, quality control data security'' and other critical areas. Wockhardt didn't respond to a request for comment.

While bad laboratory practices are usually at the root of the suspect data that inspectors are finding all over the world, in India there have also been high-profile cases of "overt and deliberate fraud," bringing the manufacturing culture there under particular scrutiny, said Janet Woodcock, the head of the FDA's center that reviews drugs. Woodcock didn't identify specific companies.

India Inspections

FDA drug-quality checks increased 18 percent in fiscal 2018 to a new peak



Source: FDA data via public records request

*Fiscal years for the federal government run Oct. 1 to Sept. 30

The agency increased inspections in India by 18 percent last year after two years of declines, underscoring the fact that India may pose the FDA's biggest challenge as it struggles to ensure drugs are cheaper but also safe.

"I don't think everything's fine, and I'm upset about it, but there's not much you can do," because India's low production costs makes its pharma industry "enormously important" to the U.S., said Bruce Downey, former chairman of an industry lobbying group who now sits on the board of Momenta Pharmaceuticals Inc., the Cambridge, Massachusetts-based generic drugmaker. "In New Jersey, there's dozens of FDA inspectors. In India, there's a dozen for the entire country."

In a statement about the adverse-event reports, Mylan lawyer Mitchell J. Langberg said that "any conclusions, inferences or extrapolations about the quality of products made by Mylan based on this data is unreasonable and unreliable." Mylan cited a disclaimer on the FDA's website saying the number of such

reports associated with a drug should not be used to determine the likelihood of a side effect occurring, and said the quality-control issues the FDA found at its factory in India did not impact the quality of its drugs.

The High Cost of Cheap Pills
A year-long investigation by Bloomberg News into the generic-drug industry shows FDA inspections at factories from West Virginia to China have found reason to doubt the data meant to prove drugs are safe and effective. This is the third of four parts.

- *America's Love Affair With Cheap Drugs Has a Hidden Cost*
- *How a Tainted Heart Drug Made in China Slipped Past the FDA*
- *The $4.3 Billion Deal That Blew Up Over Shoddy Drug Production*

The FDA uses the adverse-event-reports database to look for new safety concerns and monitor products after they've been approved. The reports have not been medically verified, according to the FDA.

What Bloomberg found in the agency's records highlights what's at stake in the questions that persist around industry-supplied data used to confirm the safety of generic drugs: When a doctor prescribes one, how do patients know it will work the way it should? If the data submitted by the drug's manufacturer can't be trusted, they don't know.

Doubts about generic-drug companies' data aren't unique to India. But when you ask veterans of India's pharmaceutical industry why the questions linger here, they use a singular term to explain it: jugaad.

The Hindi word, translated as "creative improvisation" when it was held up in the Harvard Business Review in 2010 as an example for corporate America, has been elevated to something of a national ideal in India. It's credited with the rise of the country's two global industries, technology and drugmaking. In both, Indian companies with far fewer resources than foreign rivals came up with cheaper, more effective ways of doing things that ended up being a competitive advantage.

But the word can have a darker connotation: Get it done at all costs.

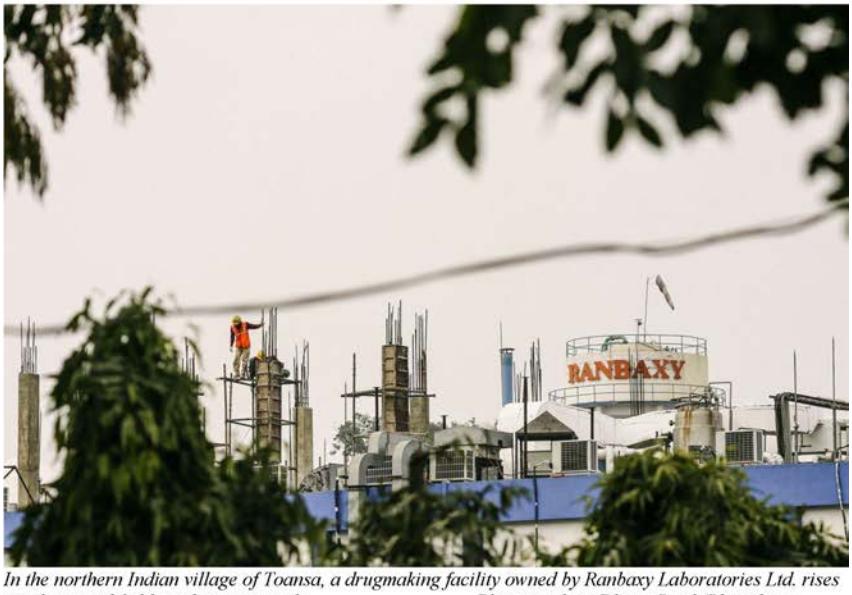
"It's kind of bending the rules, breaking the rules, and finding shortcuts—and in some cases, outright misdemeanors," said Jagdish Dore, who runs pharmaceutical-industry consultancy Sidvim LifeSciences in Mumbai. "And the pharma industry is not one where you can bypass rules and regulations."

People who closely follow the Indian business world trace jugaad's emergence to the colonial era, when laws and regulations were often in service of British interests, rather than Indian ones, and so fair game to be skirted, bent or broken. After independence in 1947, the period of heavy handed government control and regulation of the economy known as the "License Raj" further cemented a flexible approach to the rules as a precondition for success in India.

In some ways, the country emerged out of a kind of state-sanctioned jugaad. Frustrated by the high price of drugs made by foreign firms, the Indian government tweaked its laws in the 1970s so that instead of a drug itself being protected, a company could patent only the process for making it.

That meant open season on any major brand-name drugmakers' products, so long as the legions of highly trained scientists being pumped out of India's research institutes could find a different method for synthesizing them. By the time India opted back into the international patent system in 2005, the country had developed so much capacity for cheaply producing copycat drugs, it was poised to take over the global generics industry.

Today, India's thousands of drug companies not only supply the country's poor with affordable medicine, but have become a key source of drugs for the rest of the developing world. They played a central role in bringing down the price of lifesaving antiretroviral drugs that have helped contain the AIDS epidemic. Mylan's plant is a supplier of these, too. Globally, India accounts for 20 percent of generic-drug exports.



In the northern Indian village of Toansa, a drugmaking facility owned by Ranbaxy Laboratories Ltd. rises amid mustard fields and ox-cart tracks. *Photographer: Dhiraj Singh/Bloomberg*

But its drug industry also was responsible for one of the most dramatic examples of data manipulation in the history of the generics business. In 2013, New Delhi-based Ranbaxy Laboratories Ltd. pleaded guilty to the manufacture and distribution of adulterated drugs, and paid a $500 million penalty to the U.S. Justice Department, after widespread data manipulation was found at two of its factories.

India became a focus for the FDA, and regulators have uncovered a steady stream of suspicious behavior at numerous companies, from computer files found deleted to employees caught on a company's own security cameras shredding documents the night before an inspection, according to FDA inspection documents posted to the agency's website. The FDA calls these data-integrity problems.

The concerns got bad enough that Margaret Hamburg, who ran the agency under President Barack Obama, traveled to India herself in 2014 to get a handle on the problem. That year, the FDA stepped up oversight, resulting in additional sanctions in 2015, when Indian plants accounted for 60 percent of the 20 warning letters handed down from the FDA's Office of Manufacturing Quality.

The regulatory scrutiny has taken a toll on the companies. FDA warning letters bar new product launches from a facility, restraining revenue growth. Since 2015, an index of Indian pharma company stocks has

declined 25 percent on the Bombay Stock Exchange. The broader market, India's benchmark S&P BSE Sensex Index, has rallied almost as much the other way over the same period.

That's helped put pressure on the country's pharma barons—a coterie of homegrown billionaires whose net worth is tied up to a large extent in their company's stock. In the last two years, the most important executives have gathered for annual forums at an upscale hotel in Mumbai to hold forth about the primacy of a "culture of quality" to an audience of enthusiastic middle managers and visiting FDA officials.

D.G. Shah, a white-haired veteran of Pfizer's India operations who now runs the Indian Pharmaceutical Alliance, an industry body representing the largest domestic companies, has organized the panels. Shah said the root of the problem in India's generics industry is cultural, but insisted a lax attitude toward process and procedure is to blame.

"That's the lifestyle, that's the way people live in this country," he said in an interview in Mumbai. He takes as an example the perpetual traffic jam honking away outside his window, where motorists habitually violate the rules of the road, and high concrete barriers are in place to keep cars, motorcycles and scooters from seeking a shortcut by darting into oncoming traffic or up on the sidewalk.

"Culture change is not something that can happen overnight," said Shah, whose group is undertaking training programs with its member companies to help a new attitude trickle down to all employees. "Culture and behavior change requires continuous effort."

While the number of FDA inspections in India and China has fluctuated in recent years, India's share of FDA warning letters from the agency's Office of Manufacturing Quality began to decline in 2016 as companies in China received more. Last year, out of 53 warning letters issued worldwide, 10 went to drug factories in India and 16 in China.

Shah said such figures are evidence that Indian companies have made progress ensuring that a disregard for the rules doesn't make it to the factory floor.

A motorcyclist passes the Wockhardt manufacturing facility in the Chikalthana industrial area of Aurangabad, India. Photographer: Dhiraj Singh/Bloomberg

In 2016, an FDA inspector visited Mylan's flagship factory about an hour's drive outside the ancient holy city of Nashik in western India, where it makes its version of Lipitor for the U.S. According to an agency warning letter, the inspector found that quality-control technicians there had disregarded about 72 percent of failing quality checks in a six-month period—for no good scientific reason. He couldn't rule out the possibility that staff were retesting failing drugs until they passed.

Interviews with nine current and former employees at the plant produced more innocuous explanations for what contributed to the problem. They said investigating why a drug fails testing is time-consuming, and whether due to time pressure, ignorance or just laziness, it was easier to say the tester spilled some of the sample or made some other mistake and then test again. If the batch passed the second test, it was assumed to be fine.

The Mylan employees, who requested anonymity because they still work for the company or elsewhere in the pharmaceutical industry, said that members of the quality-control team at that plant faced constant pressure to get the drugs out the door as fast as possible. This made it harder to properly investigate why a batch failed.

Other times, technicians could be diligent about investigating the reason for a failed test, but not as thorough about filling out the report to document their work, either because they didn't know how or had difficulty with English. Some of the employees Bloomberg spoke to said plant managers had been aware of the problem and were instituting training courses to correct it at the time of the 2016 inspection.

Asked about the workers' comments, Mylan spokeswoman Lauren Kashtan said all medications at the company's facilities are made "under stringent processes, procedures and rigorous testing designed to ensure that they meet the highest standards for quality, safety and efficacy. Any explicit or implicit suggestion that Mylan employees circumvented data and quality systems that jeopardized the quality of the medications we manufacture—for time pressures or any other reason—is simply false."

Mylan makes its version of Lipitor for the U.S. market at this factory in Nashik, Maharashtra, India. Photographer: Dhiraj Singh/Bloomberg

When FDA inspectors visited Mylan's plant again last year, they made note of four potential violations of manufacturing guidelines, but the issue around invalidated test results was not one of them. One of the potential violations was a lack of soap and hand-drying equipment in the bathroom.

In the earlier statement from its lawyer, Mylan said last year's inspection resulted in the lifting of the FDA warning letter against its plant issued after the 2016 audit. In the intervening time, the company spent "millions of dollars" on employee training and to have a third party audit and certify its investigation results, it said. Mylan said that it had not experienced serious quality-control issues with respect to the production of its generic version of Lipitor in India, and that it also manufactures that drug in the U.S.

Another FDA inspection of the Nashik plant about a week ago "found no repeat observations from prior inspections," Kashtan said, and the facility was in compliance.

As for Mylan's version of Lipitor being more likely to be associated with adverse events than other top-selling generic versions, the company said it's more appropriate to compare its safety record with the original branded drug made by Pfizer Inc. Adjusted for the number of patients who use each version, Pfizer's is associated with adverse-event reports at a rate "thousands of times" more than Mylan's, Mylan said.

When asked about the greater number of adverse-event reports for Pfizer versus makers of generic Lipitor, an FDA spokeswoman said it was because patients often don't know they're on a generic and identify their medicine by the well-known brand name of the company that invented it, rather than the drug's chemical name used by generic companies who copy it. That means versions made by generic makers are often misidentified in the database, she said.

A spokesman for Pfizer, Thomas Biegi, said Lipitor, or atorvastatin calcium, "is the most-studied statin and has a well-established efficacy and safety profile. Since its approval in the U.S. more than 20 years ago, Lipitor has been prescribed to millions of patients and studied in more than 400 clinical trials."

To help Indian factories change their culture in the wake of the Ranbaxy scandal, FDA leadership originally planned to put more inspectors on the ground. This proved harder than expected. Instead, the number of India staff shrank from a high of 12, in 2013. to only four at one point in 2017. Eight FDA employees are stationed at the India outpost now, including two drug inspectors, the agency said.

The original argument for having foreign offices was that staff would have a chance to learn the customs of the country and build key relationships with government officials to instill best practices, said the FDA's Woodcock. Inspectors based in-country also don't need a visa for each round of inspections, while those based in the U.S. do. Countries can use visas as a way to punish the U.S. for actions they don't like, such as trade wars, and to protect their domestic businesses.

"It's very difficult to separate or segregate a particular industry or a particular factory from the society in which we live."

The problem is that the FDA can't find people who want to live in India, Woodcock said. Difficulty hiring forced the agency to close its Mumbai office in 2016.

Because of those challenges, the agency has largely ditched plans to build up offices in India and China and is instead relying on a U.S.-based cadre of inspectors who fly overseas for a few weeks at a time, she said. This cadre was supposed to number as high as 20 people, but 12 were serving in its ranks as of

December. The agency expects that number to go up to 17, and says any of its 255 drug inspectors in the U.S. can fly to foreign plants as well if needed.

Amid those staffing challenges, the number of so-called surveillance inspections the FDA has conducted in India, like the ones at Mylan's plant, have fluctuated. The number fell 7 percent in fiscal 2016 and then a further 4 percent in fiscal 2017, to 174. But in fiscal 2018, it jumped 18 percent, to 206.

About 700 Indian factories are licensed for exporting to the U.S. They sprawl across a country that could fit Texas four and a half times, where 22 major languages are spoken. Getting tens of thousands of workers, spread from tiny villages to sprawling megacities, to change their habits is a herculean task.

Rishikesha Krishnan, a professor at the Indian Institute of Management in Bangalore, related a story of one foreign regulator visiting a drug factory of a company he declined to name. The inspector's first question when he arrived after negotiating India's chaotic roads was, "Guys, how can you maintain quality in your plant if this is the way things are outside?'"

"I think this is one of the challenges the pharmaceutical industry has always faced," Krishnan said. "It's very difficult to separate or segregate a particular industry or a particular factory from the society in which we live."

—With assistance from Ed Strong, Rahul Satija, and Naomi Kresge

Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India

Massoud Motamed worked for the FDA for nearly three years as an inspector for drug plants overseas. During his time, Motamed sounded the alarm on at least two facilities, one in China and another in India, that would become part of the ongoing valsartan, losartan and irbesartan recalls. NBC News

May 10, 2019, 1:01 PM EDT

By Didi Martinez, Brenda Breslauer and Stephanie Gosk

The notice arrived at the home of Denise Schreck, a New Jersey woman who suffers from high blood pressure, last July.

"URGENT PRODUCT RECALL," blared the words at the top of the letter from her pharmacy.

The blood pressure medication used by Schreck and millions of other Americans was tainted. The culprit? A chemical with the potential to cause cancer.

Schreck went online to learn more and discovered that the generic drug, valsartan, was in fact found to contain a contaminant formerly used in the production of rocket fuel, according to a government fact sheet.

"I was just really blown away," Schreck, 51, told NBC News. "It's shocking to know that you've been taking a probable carcinogen for four years."

https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971[5/10/2019 3:35:56 PM]

For more information, tune in to NBC Nightly News with Lester Holt tonight at 6:30pm ET/5:30pm CT

Denise Schreck is one of millions of Americans who have been prescribed the blood pressure medication, valsartan
NBC News

The valsartan recall came as little surprise to Massoud Motamed, a former inspector with the U.S. Food and Drug Administration (FDA). More than a year before the notices went out, Motamed had tried to sound the alarm on what he flagged as potential systemic problems at two facilities in China and India that produce the active ingredients in generic valsartan and other blood pressure medications.

Speaking out publicly for the first time, Motamed told NBC News that the FDA ultimately overruled his recommendation to crack down on one of the plants. Perhaps more alarming, he says the issues at the two overseas drug production facilities are hardly unique.

"This is only the tip of the iceberg," Motamed said in an exclusive interview.

The valsartan case underscores a new reality in the pharmaceutical industry — a growing reliance on foreign manufacturers to provide the raw ingredients for drugs sold in the U.S. According to FDA data, roughly 85 percent of the facilities manufacturing the ingredients in American drugs are located overseas, many from China and India where production costs are low and experts say local government oversight is less stringent.

The shift has contributed to a flood of recent recalls and fueled escalating concerns about the safety of medicines consumed in the U.S.

Since last summer, drug companies have announced a total of 45 recalls of generic lifesaving blood pressure medications. They include certain versions of valsartan and two other blood pressure drugs, losartan and irbesartan, as well as other blood pressure medications that contain the recalled drugs in their formulations. The raw ingredients were all traced to overseas manufacturing sites where drugs can be processed at a lower cost than at U.S. facilities.

"Growing up, we had this saying, 'You get what you pay for,'" Motamed said. "We have that belief for everything except pharmaceuticals. If we want to drive competition and drive the price down, it comes at the cost of quality."

Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India

Massoud Motamed NBC News

For Motamed, the recalls tell only part of the story. He says a more systemic issue has largely gone unreported: FDA inspectors struggling to keep up with foreign drug manufacturers that may bury or hide problems in their production.

Last year, the FDA inspected only one in five registered human drug manufacturing facilities abroad, according to agency data.

With U.S. inspectors scrambling to review a sprawling network of overseas drug production plants, the FDA is often left to rely on the word of the facility managers, Motamed said.

"I believe it would surprise Americans how much we rely on the manufacturer and whatever they tell us to say that a drug is good or bad," the former inspector told NBC News.

The FDA also inspected only about one in five domestic drug manufacturing facilities last year, according to agency data. But unlike inspections at U.S. plants, where investigators can show up without warning and ask for more time to examine conditions if they identify potential issues, Motamed said the foreign site reviews are often hobbled by language barriers and time constraints.

"Say I'm at a domestic facility and I tell my supervisors that I'm finding all these problems and I need more time to inspect. That happens — no issue," Motamed said.

"The same is not true of a foreign facility. I've had inspections where I really could have benefited from the extra time and I knew there were problems to be uncovered, but I had to leave the country."

Motamed spent three years as an FDA investigator, working mainly overseas to inspect foreign manufacturing facilities. A Texas native with a Ph.D. in biochemistry, Motamed, 34, joined the agency driven by a desire to contribute to the field of public health.

He had been in the role for more than two years when he went to inspect the Zhejiang Huahai Pharmaceutical plant in Linhai, China — the company that produced the tainted ingredients in Schreck's recalled medication — in May 2017.

Motamed's four-day inspection turned up a series of alarming issues that he later outlined in official reports. Facilities and equipment not maintained. Anomalies in testing not investigated. And "unknown

impurities" dismissed as laboratory error.

After his visit, and as first reported by Bloomberg, Motamed recommended that a warning letter be sent to the firm — an official action that bars the company from gaining the approvals to produce new U.S. drugs at the facility, until it resolves the issues.

But three months later, he was overruled by FDA management. The FDA decided to allow Zhejiang Huahai to voluntarily fix the problems on its own, the agency wrote in an official document obtained by NBC News, citing the firm's compliance history and mostly "adequate responses" to impurities in their testing.

"There are many factors that inform the FDA's decisions at a given time regarding what action to take following an inspection," the FDA said in a statement to NBC News. "We make those decisions in the interest of patient safety based on all information available to us, including evidence collected during an FDA inspection and a manufacturer's proposed corrective actions."

After facing criticism over its handling of the case, the FDA said it would have been "unlikely" to catch the impurities at the source of the recall during a routine inspection.

"Nonetheless, our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise," reads a January 2019 FDA press release.

In a statement to NBC News, Zhejiang Huahai said it's "working closely with regulators here and abroad to evaluate the source of the impurities that resulted in the recall" and is determining if "any modifications to its manufacturing processes are necessary."

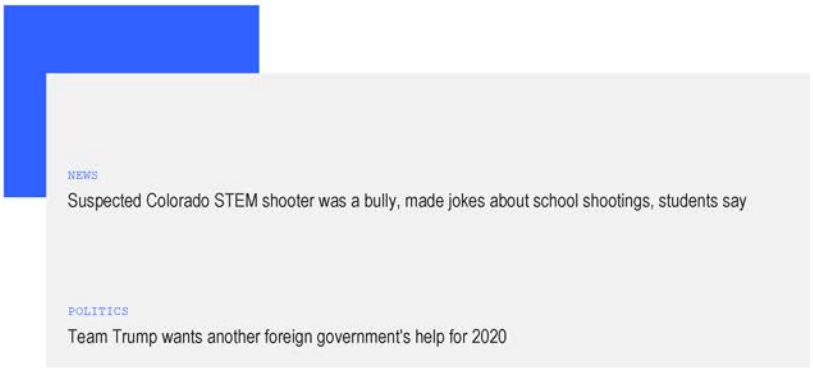
Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India

Denise Schreck got the notice from her pharmacy in July that her blood pressure medication was being recalled du
an "unexpected impurity" in her medication in the form of a probable human carcinogen. NBC News

The problems were not confined to the facility in China. While investigating a drug production factory in India, Hetero Labs Limited, in December 2016, Motamed discovered what appeared to be a brazen attempt to cover up issues at the plant.

"I was going to the bathroom and I kept seeing that people were going into an archival room. And that's not generally typical," Motamed said.

He decided to review the firm's closed circuit TV footage. What the inspector saw next shocked him.



Motamed watched footage of individuals shredding company documents four days before his arrival, the inspection report says.

"They were staying up all night shredding extensive amounts of documents right before our audit," Motamed said. "...It means there are systemic issues."

"It's one of the more concerning findings I've had over the years," the former inspector added.

The FDA eventually sent a warning letter to Hetero in August 2017, citing "significant violations of current good manufacturing practice." Some 19 months after Motamed first flagged suspicious activity at the plant, Hetero was found to be one of the sources of the contaminated drug ingredients for sale in the U.S.

Hetero did not respond to several requests for comment by NBC News.

In the case of valsartan products, the FDA said last August that more than half of all the medication sold in the U.S. was being pulled from store shelves.

While it's unknown exactly how many people have been impacted by the recalls, the sheer demand for the drugs suggest it could reach into the millions. In 2016, 1.6 million people purchased valsartan and 9.2 million bought losartan, according to data provided by the U.S. Department of Health and Human Services.

The recalls create a vexing challenge for consumers like Don Grybb, who said he struggled to find a suitable alternative after finding out that his valsartan medication was being pulled from store shelves.

"Almost from prescription to prescription, I would find significant changes in my blood pressure," said Grybb, 68, of Michigan.

Don Grybb said he was made aware of the recent valsartan recall when he got a call from his pharmacy telling him that they couldn't refill his medication. Courtesy of Don Grybb

The FDA and outside healthcare professionals have warned consumers against suddenly stopping their medication due to the recall, saying that the short-term risks outweigh the potential impact of consuming the recalled medication.

The uncertainties surrounding the medications also pose challenges to doctors.

"It's hard to know what to prescribe patients," said Dr. Randall Zusman, a cardiologist at Massachusetts

General Hospital Heart Center in Boston. "You want to assume it's safe and effective. You don't want to feel like you are prescribing something that causes harm."

The FDA says the overall risk posed by the impurities is small. For valsartan, FDA testing found the pills contained somewhere between three and 210 times the agency's acceptable level for NDMA, the probable carcinogen at the center of the recall. If 8,000 people took the highest dose of the contaminated drug daily for four years, the FDA estimates, there may be one additional case of cancer over the lifetimes of those people.

"This is troubling to us and we know it's troubling to the public," the FDA said in a statement. "The concern is appropriate."

Experts said the contaminants are still powerful at low levels. "This is well beyond the risk that government agencies typically deem acceptable," said Lisa Lefferts, senior scientist at the Center for Science in the Public Interest. "While most people won't get cancer from the contaminants in these pills, it's an unacceptable risk, and avoidable."

The FDA has issued a list of medications free of the probable carcinogens and says it has been working to mitigate and prevent shortages.

"Our first action was to immediately undertake a major operation to investigate and to identify the root causes of the presence of these impurities and to work with companies to address the risks that the impurities posed to patients," Dr. Janet Woodcock, the FDA director for the Center for Drug Evaluation and Research, said in a statement to NBC News.

Dozens of consumers have now gathered to sue nearly every company involved in the recall through a consolidated multidistrict litigation case in New Jersey.

"There are a lot of things that could have been done to prevent something like this," Daniel Nigh, an attorney for the plaintiffs, told NBC News.

The Association for Accessible Medicines, the trade group for generic drug manufacturers, said its "member companies with affected products voluntarily recalled their medicines containing valsartan and have worked closely" with the FDA.

"Patients in the United States can be confident that the medicines they take are safe and effective," the group added. "Manufacturers of generic medicines and the Food and Drug Administration work to ensure

that prescription drugs meet the same high-quality standards regardless of where they're manufactured."

Motamed left the FDA in 2017, disillusioned over his experience trying to police a sprawling industry in what he described as a "cat and mouse" game where companies do what they can to conceal problems from the FDA. He believes the agency needs to hire more qualified investigators and needs to conduct more inspections of the overseas facilities producing drug ingredients.

Now working for the private pharmaceutical sector in India, Motamed said he's speaking out to raise awareness about the risk of tainted drugs.

"I think there's a significant portion which, if we test it here in the U.S., would not pass," Motamed said.

As for Schreck, the anxiety brought on by the valsartan recalls has prompted her to stash her bottle of pills in a small brown cabinet above her kitchen sink.

Why? She sees it as evidence that could be used in a court of law in the event that cancer were to infect her body one day.

"I hate to think that because of this I run an extra risk of developing cancer," Schreck said. "But it is my proof."

Didi Martinez

Didi Martinez is a researcher with the NBC News Investigative Unit.

Brenda Breslauer

Stephanie Gosk

STAT

In generic drug plants in China and India, data falsification is still a problem

By Katherine Eban *and* Sony Salzman

October 29, 2019

A pharmacist works in a lab where medicines are being made on the outskirts of Mumbai, India. *Rafiq Maqbool/AP*

As the generic drug industry faces allegations of data manipulation, headlines about carcinogen-tainted[2] blood pressure medicine, and an intensifying probe by the House Energy and Commerce Committee, whose health subcommittee is holding a hearing on Wednesday[3] on safeguarding our global drug supply, generic drug industry lobbyists are fighting back.

They claim[4] that low-cost drug makers operating overseas — where the majority of our generic drugs are made — follow the same intricate rules as U.S.-based drug makers. They argue[5] that instances of manufacturing fraud or negligent practices are a thing of the past, having ended largely in 2013 when India's largest drug company, Ranbaxy, pleaded guilty in the United States[6] to seven felonies related to falsifying manufacturing data.

The Food and Drug Administration, also on the defensive, has been quick to reassure consumers and Congress[7] that its regulatory system of data review and inspections is effective regardless of where drugs for the United States are made.

But our analysis of the FDA's own records reveals 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. With the help of FDAzilla[8], a leading data analytics company, we analyzed 5 1/2 years of FDA inspection records, from 2014 to the present, for four major markets: China, India, Europe, and the United States.

Related: [9]

The Indian pharmaceutical industry is in denial over drug-quality charges [9]

The data show significantly greater falsification or manipulation of manufacturing data in Indian and Chinese drug plants. "Egregious data integrity violations are alive and well, especially in China and India," said Michael de la Torre, chief executive officer of FDAzilla's parent company, Govzilla. "While the U.S. and Europe are not immune to serious data integrity violations, China and India are at least twice as likely to have these issues."

Out of more than 12,000 FDA inspections of drug plants in the United States, about 15% uncovered violations of the FDA's data integrity rules. These

stipulate that all manufacturing data must be preserved — unaltered — and made available to regulators. In India, about 25% of the plants inspected committed some sort of data violation, while in China, that figure hovers just above 32%.

Country	Number of inspections	Number (percentage) of violation forms (Form 483[10]) issued	Percentage of Form 483s that cite data integrity violations	Percentage of Form 483s that cite data manipulation
China	916	617 (67.4%)	32.4%	48.1%
India	1,693	976 (57.6%)	25.3%	44.0%
Europe	2,969	1,445 (48.7%)	17.3%	35.6%
USA	12,000	6,794 (56.6%)	14.7%	25.9%

While this analysis reflects a serious problem, it likely understates the severity. The FDA is failing to detect a significant amount of fraud in overseas plants because of the way it conducts those inspections. In the United States, FDA investigators show up unannounced for inspections. But abroad, the agency has chosen to pre-announce its inspections, a system that gives plants time to clean up any evidence of unsanitary conditions, wrongdoing, or data manipulation.

In 2014, when the FDA attempted a short-lived experiment of giving Indian drug plants only short or no advance notice of inspections, the serious violations uncovered by its investigators rose by almost 60%[11].

The glaring shortcomings of the FDA's decision to pre-announce overseas inspections, exposed in "Bottle of Lies: the Inside Story of the Generic Drug Boom,"[12] which one of us (K.E.) authored with help from the other (S.S.). These inspections are now under review by the House Energy and Commerce Committee's oversight and investigations subcommittee.

But these numbers tell only part of the story. We also wanted to understand if there is a difference not only in the *rate* of data violations but in the *nature* of the wrongdoing. Some practices, like multiple lab technicians using the same log-in information, suggest unprotected computer systems. That might amount

to negligence. But other practices, like lab technicians deleting irregular test results or discarding raw data, suggest fraud. Here, too, our analysis shows that data integrity violations in India and China are more egregious than they are in the United States and Europe.

To distinguish negligent practices from egregious ones, we worked with FDAzilla to identify key words in the FDA's inspection reports, such as falsification, destruction, and backdating. By comparing inspection reports, we discovered that in the United States about 28% of plants cited for data integrity problems exhibited truly deceptive behavior. In India, that number rose to 55%, and in China, to 65%.

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[15] to justify the release to market of its diabetes drug glimepiride. 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.

At the Cleveland Clinic, as "Bottle of Lies" chronicles, heart transplant patients whose anti-rejection medication was working fine ended up suffering organ rejection after taking an ineffective Indian-made immunosuppressant.

At the manufacturing plants themselves, data integrity violations can mean profound deceit: tearing up records of failing drug tests and smuggling them from the plant; or inventing data to indicate that a plant is sterile, without actually doing the required microbial testing of the surfaces, air, and water.

Related: [16]

Presidential candidates aren't talking about drug shortages. They should be [16]

The FDA recently announced[17] what appeared to be great news: It had approved 1,171 new generic drug products for fiscal year 2019, a new record. But this week, as congressional leaders hold yet another hearing on the safety of our drug supply and the adequacy of the FDA's regulatory system, they need to consider an unpleasant truth: The overseas manufacturers that are ostensibly saving us from runaway drug prices are actually exposing us to growing risk of getting drugs with undetected impurities or faked results.

There is no question that Americans need more affordable medicines. But to ensure high quality, the FDA needs to overhaul its overseas inspection program — and it should start by ending the practice of the advance-notice inspections for which plants prepare. In March, for example, an FDA investigator inspecting the NingBo Huize Commodity Co., in Zhejiang, China, found that the plant had falsified all sorts of documents[18]: cleaning validation reports, batch records, and annual reports. Under questioning, the plant's general manager confessed that the documents had been faked "for the purpose of this inspection," according to an August warning letter.

In today's interconnected, global drug supply chain, the FDA's regulatory honor system — which relies on company-submitted data and pre-announced inspections and does not systematically test drugs to verify their contents — is no longer adequate. Americans should demand that the FDA and its investigators police overseas manufacturing plants and their drug products with the same rigor — and using the same standards — as they do domestic ones.

Katherine Eban is an investigative journalist and the author of "Bottle of Lies: The Inside Story of the Generic Drug Boom"[12] *(HarperCollins, 2019). Sony Salzman is a freelance science and medical journalist who worked as a researcher on "Bottle of Lies."*

About the Authors

Katherine Eban

@KatherineEban[19]

Sony Salzman

sonysalz@gmail.com[20]
@sonysalz[21]

Tags

Links

1. https://www.statnews.com/category/first-opinion/
2. https://www.statnews.com/pharmalot/2019/10/21/consumers-sue-sanofi-and-other-drug-makers-over-zantac-link-to-a-carcinogen/
3. https://energycommerce.house.gov/committee-activity/hearings/hearing-on-safeguarding-pharmaceutical-supply-chains-in-a-global-economy
4. https://www.pharmamanufacturing.com/articles/2019/making-the-case-for-indian-generic-manufacturing/
5. https://www.orfonline.org/expert-speak/pharma-conundrums-bottle-lies-51847/
6. https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false
7. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-drug-evaluation-and-research-0
8. https://fdazilla.com/
9. https://www.statnews.com/2019/07/22/indian-pharmaceutical-industry-drug-quality-charges/
10. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions
11. https://www.newsweek.com/2019/07/19/bottle-x-exposing-impurities-generic-drug-business-1446934.html
12. https://www.harpercollins.com/9780062338785/bottle-of-lies/
13. https://www.statnews.com/signup/
14. https://www.statnews.com/privacy/
15. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/indoco-remedies-limited-575313-07162019
16. https://www.statnews.com/2019/08/09/drug-shortages-presidential-candidates-policy/
17. https://www.fda.gov/news-events/press-announcements/statement-continued-progress-enhancing-patient-access-high-quality-low-cost-generic-drugs
18. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/ningbo-huize-commodity-co-ltd-581345-08022019
19. https://twitter.com/KatherineEban
20. https://www.statnews.com/2019/10/29/data-falsification-still-problematic-china-india-generic-drug-plants/mailto:sonysalz@gmail.com

21. https://twitter.com/sonysalz
22. https://www.statnews.com/tag/ethics/
23. https://www.statnews.com/tag/pharmaceuticals/

U.S. GOVERNMENT ACCOUNTABILITY OFFICE

441 G St. N.W.
Washington, DC 20548

January 22, 2020

The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

Following the December 10, 2019, hearing held by the Subcommittee on Oversight and Investigations, *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program*, we received questions for the record from Subcommittee members. This correspondence provides our responses to these questions. If you or your staff have any questions or need additional information, please contact me at 202-512-7114 or DeniganMacauleyM@gao.gov.

Sincerely yours,

Mary Denigan-Macauley
Director, Health Care

Enclosure

cc: The Honorable Greg Walden, Ranking Member, Committee on Energy and Commerce
The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations
The Honorable Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program"

December 10, 2019

Mary Denigan-Macauley, Ph.D
Director, Health Care,
Government Accountability Office

The Honorable Brett Guthrie (R-KY)

1. **GAO has recommended that FDA take steps to improve the accuracy and completeness of information in its catalog of drug firms subject to inspection. In 2010 and 2016 reports, GAO found that FDA took steps to improve information accuracy. What steps remain for FDA to improve the accuracy and completeness of information in its catalog of drug firms subject to inspection?**

We have had concerns since our 1998 report about the information FDA maintains on drug establishments subject to inspection and have made related recommendations.

In our 2010 report we described steps FDA was taking to improve the information in its databases that identify registered foreign establishments and products imported to the United States and are used to create a catalog of establishments subject to inspection. For example, we reported that FDA began requiring registration information to be submitted electronically. We also reported that FDA contracted with external organizations to conduct site visits to verify the existence of foreign establishments registered with the agency and verify the products manufactured by those establishments. Finally, we reported that FDA initiated a project to identify and remove duplicate records from its import database.

In our 2016 report we described additional steps FDA had taken to improve the accuracy and completeness of its catalog of foreign drug establishments. First, we reported that, in accordance with the Food and Drug Administration Safety and Innovation Act, FDA began requiring establishments to provide a unique facility identifier during their annual registration process. We reported that FDA then used this number to automatically validate registration information using a Dun and Bradstreet database. We also reported that FDA added two foreign inventory coordinators to incorporate foreign registrations and annual updates into FDA's master inventory and established a data governance board to define standards, best practices, and policies for inventory data management.

Despite these efforts, we still have concerns about the accuracy and completeness of the information FDA maintains on drug establishments subject to inspection. In our 2019 testimony we reported that recent declines in the count of foreign inspections conducted by FDA were due,

in part, to data inaccuracies that affected its process for selecting establishments for inspection. Specifically, we noted that as part of its initiative to inspect approximately 1,000 foreign establishments that lacked an inspection history, FDA selected establishments for inspection but then determined that a sizeable percentage were not actually subject to inspection. FDA has noted continued challenges related to maintaining complete and accurate information on foreign drug establishments. For example, the agency reported that in fiscal year 2018 it removed approximately 50 percent of registered South Korean drug manufacturing establishments from its catalog because they did not have product in the U.S. market and did not need to be registered.

2. **My understanding is that the GAO plans to evaluate the FDA's risk-based selection model that is used to prioritize inspections. What questions does GAO have about the risk-based selection model? As part of the risk-based selection model evaluation, will GAO assess the potential benefits of using alternative methodologies or models, such as a predictive risk model?**

To prioritize establishments for surveillance inspections—that is, inspections used to ensure drugs already on the market are manufactured in compliance with FDA regulations—FDA applies a risk-based site selection model to its catalog of establishments subject to inspection. The model is used 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 experience 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.

In our 2019 testimony we reported that a majority of foreign and domestic inspections from fiscal year 2012 through 2018 were surveillance inspections. Given FDA's history of challenges related to the management of information on drug establishments, reviewing the quality of information underlying the model used to select establishments for surveillance inspections could be important to ensure that the risks of foreign and domestic establishments are assessed in equivalent ways. We are exploring methodologies to allow us to further explore FDA's risk-based model. We would be happy to brief you on our scope, methods, and time frames, once established.

3. **Has the FDA provided any data or studies to the GAO that support conducting preannounced inspections in foreign drug inspections over unannounced or short notice inspections?**

In our 2008 report we found that, unlike domestic inspections which are almost always unannounced, FDA generally provides advanced notice of inspections to foreign establishments.

In our 2019 testimony, we reported that FDA stated that it generally preannounces its foreign inspections to avoid wasting resources and to obtain the assistance of foreign establishments when making travel arrangements. 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 FDA's database does not include a data field to track whether an inspection is

announced or unannounced. However, officials told us that the agency plans to include a new data field that would enable the agency to track whether an inspection is preannounced or unannounced.

Based on our interviews with investigators in FDA's dedicated foreign drug cadre and investigators based in its China and India offices, we reported in our 2019 testimony that a downside to preannounced inspections is that the advanced notice provides establishments time to fix some problems before the investigator arrives. FDA expects establishments to be in a constant state of compliance with current good manufacturing practice (CGMP) regulations, and several investigators told us that an investigator is more likely to see the true operating environment of an establishment during an unannounced inspection. Although most of the investigators we interviewed told us that unannounced inspections are preferable to preannounced inspections, some investigators said that it was still possible to identify serious deficiencies during a preannounced inspection.

4. **In 2016, GAO reported that FDA had yet to determine whether the foreign offices meaningfully contribute to drug safety, because FDA has no formal process for assessing the offices' contributions. What are the GAO's recommendations for FDA to track foreign office accomplishments to assess the extent to which those offices help ensure drug safety?**

GAO has made two recommendations directing FDA to assess whether the foreign offices are fully able to meet their mission of helping to ensure the safety of imported drugs.

- First, in a 2010 report, GAO recommended that FDA develop a set of performance goals and measures that can be used to demonstrate the foreign office contributions to the long-term outcomes related to the regulation of imported products, and that foreign office activities are coordinated with the centers and Office of Regulatory Affairs.

- Second, in a 2016 report, GAO recommended that FDA assess the effectiveness of its foreign offices' contributions by systematically tracking information to measure whether the offices' activities specifically contribute to drug safety-related outcomes, such as inspections, import alerts, and warning letters. We have designated this recommendation as a "priority recommendation," meaning that GAO believes this recommendation warrants priority attention from the heads of key department and agencies, and we will continue to monitor the agency's progress towards implementing this recommendation.

While FDA has not fully implemented these recommendations, it has taken some actions in response. Specifically, as of June 2018, FDA stated that it has developed new performance measures for the foreign offices as well as a monitoring and evaluation plan. It has also strengthened communications and collaboration between the foreign offices and other offices within FDA and conducted an assessment of the foreign offices to help set their objectives and ensure the right balance of personnel, skillsets, and resources. Despite this progress, FDA still needs to continue to develop intermediate outcomes to link with final outcomes to fully implement these recommendations. We believe it is important for FDA to track these types of outcomes, and for the agency to determine how their performance measures—whether the

existing ones or those currently being tested—can be used to demonstrate such results. Having performance measures that demonstrate results-oriented outcomes will better enable FDA to meaningfully assess the foreign offices' contributions to ensuring drug safety.

5. **In its 2010 report, the GAO recommended that FDA develop a strategic workforce plan to help recruit and retain foreign office staff. FDA released such a plan in March 2016, but there are still longstanding vacancies in the foreign offices. Your written testimony states that these vacancies raise questions about the implementation of FDA's workforce plan. What were the problems in the implementation?**

    a. **In addition to implementation issues, do you have any additional comments on FDA's workforce plan?**

    b. **What does FDA need to do to improve retention and management of inspectors, particularly in foreign offices?**

In our 2010 report, we recommended that FDA develop a strategic workforce plan for the 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. As you state, 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 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 testimony, while vacancy rates in 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, 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 used for 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.

In addition to these challenges with hiring and filling vacancies, we also noted in our 2019 testimony that investigators face certain challenges when they conduct foreign inspections, such as long hours and a lack of flexibility with overseas travel for ORA investigators based in the United States. We plan to continue to examine these issues in our ongoing review.

The Honorable H. Morgan Griffith (R-VA)

1. **Besides banning imports to the United States, how can FDA protect the supply chain when a foreign facility refuses an FDA inspection? When an importation ban is placed on a manufacturer, what does FDA do about API it has already introduced into the United States?**

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) gave FDA new authorities to address challenges related to an increasingly global drug supply chain. Specifically, Section 707 of FDASIA allows the agency to deem adulterated any drug that is manufactured in an establishment that delays, limits, denies, or refuses to permit FDA entry or inspection. In October 2014, FDA issued final guidance on the types of conduct and circumstances that the agency considers to constitute delaying, denying, limiting, or refusing a drug inspection, which could result in a drug being deemed adulterated.[1] FDA's final guidance specifies that the delaying, denying, limiting, or refusing a request for records in advance or in lieu of an inspection may also result in a manufacturer's drugs being deemed adulterated. Drugs that have been deemed adulterated are refused entry into the United States.

We have not otherwise examined the types of actions that FDA is authorized to take against a foreign establishment if it refuses an FDA inspection, or what happens to drug products that have already been introduced into the United States when an importation ban is placed on the establishment manufacturing those products. We would be happy to discuss future work in this area with your staff.

[1]FDA guidance defining the types of actions, inaction, and circumstances that FDA considers to constitute a delay, denial, limit, or refusal to entry or inspection is publically available on FDA's website: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/circumstances-constitute-delaying-denying-limiting-or-refusing-drug-inspection

October 15, 2020

The Honorable Frank Pallone
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Pallone:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the December 10, 2019, hearing before the Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, entitled "Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

Andrew Tantillo
Acting Associate Commissioner for
Legislative Affairs

cc: The Honorable Greg Walden, Ranking Member, Committee on Energy and Commerce

The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations

The Honorable Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Your questions are restated in bold, below, followed by FDA's response.

The Honorable Frank Pallone, Jr. (D-NJ)

1. **A previous report from the Government Accountability Office raised certain concerns about post-inspection processes, such as delays in the Center for Drug Evaluation and Research (CDER) receiving inspection reports and subsequently taking action against firms if necessary. This report also indicated that CDER sometimes did not verify that foreign firms took the corrective actions mandated by the Food and Drug Administration (FDA) after an inspection.**

   a. **When results from an inspection of a foreign firm indicate that corrective action is needed, does FDA always conduct a follow-up inspection to determine whether that firm took those corrective actions? If not, under what circnmstances does FDA decide not to conduct a follow-up inspection?**

   b. **What actions other than follow-up inspections does FDA take to confirm whether a foreign firm has instituted necessary corrective actions?**

   Following an inspection in which results indicate that corrective action is needed, firms have an opportunity to provide information to FDA regarding their proposed corrective actions as well as supporting information to demonstrate that the corrective actions are appropriate and sufficient to address the observations. FDA reviews this information when classifying the inspection and determining whether any advisory or enforcement actions may be necessary. Information regarding the inspection observations is also incorporated into a dossier for the facility so that on subsequent inspections investigators can verify implementation of the corrective actions.

   In general, FDA conducts a follow-up inspection to evaluate corrective actions for inspection outcomes classified as "official action indicated;" if classified as "voluntary action indicated," the follow-up verification of corrective actions by inspection usually takes place during the next surveillance inspection. If a firm indicates that they no longer manufacture and distribute product for the U.S. market, FDA will continue to monitor import entries to confirm the firm is no longer exporting, rather than conduct a follow-up inspection. FDA may also list a facility on import alert for appearing to violate applicable statutory or regulatory requirements, for example, for refusing an inspection or not conforming with current good manufacturing practice (CGMP) requirements. The import alerts inform FDA field staff of evidence that the products appear to be violative. 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 CGMPs. However, if a facility on import alert does not provide any indication that they have remediated problems and are ready for re-inspection, FDA generally will not conduct a follow-up inspection and the facility will remain on import alert.

2. **During the hearing, Ranking Member Guthrie asked you about whether FDA had evaluation criteria to determine the effectiveness of its foreign drug inspection program.**

You indicated that FDA needs to address this issue. Does FDA have plans to create evaluation criteria for its foreign drug inspection program? If so, when does FDA plan to implement such criteria, and what types of factors will be included in these criteria?

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.

3. **During the hearing, you indicated that you would prefer that FDA use a predictive model, as opposed to the site selection model currently used by FDA. Please explain what type of predictive model you envision and why you prefer this type of model to the site selection model currently used by FDA.**

The current site selection model is a risk-based prioritization model. For the future, FDA seeks to implement a predictive risk model to select drug manufacturing establishments for inspection. This statement was in the context of describing the required elements for such a model. Specifically, FDA would likely need manufacturing volume data for each product from each facility and reliable quality indicator data (e.g., quality metrics). Although the current prioritization model is risk-based, it does not predict risk for sites. The predictive risk model would be preferable because its output could be explicit about the level of risk posed by each establishment. However, characterizing risk requires volume information to understand the scale of impact and quality indicator data to describe the state of quality. Although we can describe the locations of API manufacturing facilities, we cannot determine with any precision the volume of APIs that a foreign country is actually producing, or the volume of APIs manufactured in a foreign country that is entering the U.S. market, either directly or indirectly by incorporation into finished dosages.

The Honorable Brett Guthrie (R-KY)

1. **Foreign firms are able to ship over-the-counter drugs and raw materials into the U.S. without FDA registration or iuspection. Does FDA see that process as a vulnerability and, if so, what is being done to evaluate that process to make any necessary changes?**

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 assessment 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. Notable examples of these types of drugs include active pharmaceutical ingredients (APIs) for compounding, and many over-the-counter (OTC) drugs marketed through conformance with OTC "monograph" regulations (including the APIs used in such OTC drug products). 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.

Domestic and foreign establishments that manufacture, prepare, propagate, compound, or process drugs in the U.S., or drugs offered for import into the U.S., are required to register with FDA and list such products with FDA. However, some API producers shipping to OTC drug product manufacturers are not known to FDA, particularly where a foreign API producer supplies an API to a manufacturer of a drug product subject to an OTC monograph that is also located outside the U.S. When the API, alone, is not shipped to the U.S., some foreign API producers do not register with FDA and may not know the manufacturer will distribute the product in the United States. The same situation exists for some finished and unfinished drug products that are not directly shipped to the U.S. but are ultimately distributed to U.S. consumers. The Administration's FY2020 Budget Justification[1] included a legislative proposal to address this issue and require more accurate supply chain information.

2. **With regard to the Site Selection Model used to select drug firms by prioritizing those with the highest risk, how has the FDA validated that this model to ensure that FDA is properly scoring the firms with the highest risk?**

In January 2017, the Site Selection Model (SSM) was subjected to an independent external peer review (managed by a contractor) by three experts in risk modeling. The model was evaluated and recommendations for improvement were provided and implemented.

3. **Would adding source information to drug labels to include all information about where the ingredients were manufactured raise consumer awareness and better help put pressure on manufacturers to ensure the purity and safety of their drugs? Has the FDA considered funding studies to determine the usefulness to consumers and physicians of adding sourcing information to drug labels?**

Drug products usually contain multiple ingredients, active and inactive, and often these ingredients are sourced from different suppliers from batch to batch, depending on availability and cost. Reflecting the source of the ingredients in product labeling could potentially result in new labeling for each batch. Additionally, because the status of a facility can change over time, a source that is acceptable today may not be acceptable six months from now, and vice versa. It would be extremely difficult for someone without intimate knowledge of the drug inspection process to make an informed decision on their own as to the acceptability of the source of each of the ingredients.

---

[1] *https://www.fda.gov/media/121408/download*

Current regulations require drug product manufacturers to test all components (ingredients) before use in manufacturing. FDA is exploring options to modify existing policies with the aim of promoting more mature quality management systems as well as oversight of component/ingredient suppliers. Additionally, FDA is pursuing the generation, collection, and use of specific quality metrics (i.e., quality indicators) that help ensure manufacturers are controlling more critical risks to drug quality.

4. **The FDA just added a data field this month to its data system to capture when inspections are announced or unannounced. Does FDA plan to populate that data historically and if so, to what date?**

The data field has not yet been added to eNSpect (the FDA IT system used to generate inspection reports) but will be implemented in a future release. When it is implemented, we do not plan to populate any historic data.

   a. **What other data fields were added for collection?**

   No other data fields have been added at this time; however, as noted above, a data field to track whether an inspection was announced or unannounced will be implemented in a future release of eNSpect.

5. **Does FDA think there is a conflict of interest when the firm being inspected provides the translator for FDA's inspection?**

During an inspection, FDA investigators should be able to communicate directly with the firm to ensure that the information collected and the messages conveyed are accurate, complete, and fully understood. Language differences can be an impediment to such communication. Therefore, it is important to have translators on hand that can serve as an accurate conduit for our investigatory staff. When possible, FDA uses independent translators. However, that is not always feasible.

6. **What resources does FDA have to pay for its own translators? How much of these overall resources are used to support translators in foreign drug inspections?**

ORA obligated $2.1M in FY18 and $1.5M in FY19 for translation services. Of the total obligations, approximately three percent are related to drug inspections.

In some cases, FDA can contract, through an Inter-Agency Agreement (IAA) with the State Department, for an interpreter to accompany the investigator on inspection when needed.

In FY18, FDA contracted interpreters to accompany investigators on 89 foreign trips with an average cost of $1,681 per day, with a total average cost of $20,000 per trip. The cost varied across different countries and across languages spoken, but in total the Agency spent over $1.7 million on Agency-contracted interpreters in FY18.

Most of the inspections utilizing the IAA interpreter services in FY18 were in the foods program (79 trips) whereas there were only five drug-related trips that utilized the IAA interpreter services, at a total cost of approximately $100,000.

7. **FDA reported to GAO that a primary data source used to calculate the inspection risk model included nearly 1,000 firms that did not actually require FDA inspection. FDA called those firms "washouts." How were the nearly 1,000 "washout" drug manufacturers FDA discovered when the risk model scores were calculated? In your slide presentation, did the baseline data used for the information include "washouts"? If so, please explain washouts. How much greater risk weight in the risk model is given to manufacturers of finished drug products than to manufacturers of APIs?**

Some level of 'washout' of assigned inspections is always expected. FDA has been improving its vetting process to minimize the number of washouts. Washouts occur because the establishments are not inspection obligations for FDA due to: a firm going out of business, a firm no longer producing for the U.S. market, data errors, and registration errors. Firms self-register and there is no barrier or fee for registration, so some foreign firms register as a means of self-promotion. It is then incumbent upon FDA to determine if the establishment meets the criteria for an inspection obligation. If it does not, it becomes a washout.

With regard to the number of washouts, please refer to Dr. Janet Woodcock's December 10, 2019, testimony, which states that the number of washouts was 359 out of a total of 965 sites never previously inspected:

> CDER's Catalog showed that as of July 2016, there were 965 foreign manufacturing facilities that had never been inspected by FDA. By the end of FY 2019, FDA had inspected 495 or 51 percent of these previously uninspected facilities (See Figure 4). An additional 359 facilities (37 percent) were removed from the Catalog because they were no longer part of FDA's inspection obligations for a number 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 six percent of the facilities had refused inspection; 37 or four 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 22 or two percent had no drug shipments.
>
> The SSM does not have different weights, per se, for finished dosage forms (FDF) and API sites. Both are considered "Drug Manufacturers" by the SSM. The model differentiates manufacturers based on the inherent product risk associated with the drugs they make. In general, FDF sites may have higher scores than API sites; but this is because of the higher-risk products (e.g., narrow therapeutic index drugs (i.e., drugs that must be made to tighter assay specification), drugs used in medical emergencies) made at the facility, not because it is an API or FDF facility.

8. The FDA believes that its system for inspecting foreign drug plants – which involves reviewing company-submitted data and conducting pre-announced inspections – is adequate for ensuring quality. Yet that system failed to detect the presence of carcinogens in blood-pressure medicine taken by millions of Americans and potential carcinogens in the diabetes treatment drug Metformin. Should the FDA begin to verify quality, for example by launching a system of chemical testing more imported pharmaceuticals for purity, API amount, and dissolution rate?

FDA has an active program for sampling and testing drugs to verify they meet required quality attributes and specifications. FDA also collaborates with foreign partners by sharing data, especially about critical issues of safety and efficacy. For additional information, please see Dr. Janet Woodcock's statement on December 5, 2019.[2]

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. No single test can detect all potential impurities. Tests are selected based on assessments of what impurities may develop as a result of the manufacturing process. In other words, it generally needs to be recognized that there's a risk of an impurity occurring as a result of a manufacturing process to know the impurity that should be tested for. Before we undertook this analysis, neither regulators nor industry fully understood how nitrosamines could form during these manufacturing processes.

Some have raised the question of why we do not test every drug product before it enters the United States. FDA performs thousands of tests on drug products each year pre- and post-market. Only a small percentage (about one percent) of drugs that are tested fail to meet the established quality specifications. 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. For example, in 2018 there were almost 186 trillion tablets and capsules on the U.S. market. The current approach is effective and efficient.

9. After September 11, 2001, then-HHS Secretary Tommy Thompson asked Congress to add 600 more inspectors and laboratory personnel,[3] increasing the total FDA field staff to about 4,000 in 2002. In 2007, the *New York Times* reported that the FDA budget did not keep up with inflation and the field staff decreased 13% to 3,488, even fewer than the 3,500 original staff totals in 2002 before the hiring increase.[4] The 2012 enactment of the Generic Drug User Fee Act added resources for FDA to support the hiring of more drug inspectors, and yet in the last few years there has been a sharp decrease in the number of drug inspectors down from 245 inspectors to 188 since 2016. FDA historically has struggled to hire more inspectors, even with user fees. Given this

---

[2] *https://www.fda.gov/news-events/press-announcements/statement-janet-woodcock-md-director-fdas-center-drug-evaluation-and-research-impurities-found.*

[3] Government Accountability Office, *Food Safety: FDA's Imported Seafood Safety Program Shows Some Progress, but Further Improvements Are Needed* (Jan. 2004) (GAO-04-246).

[4] *Food Imports Often Escape Scrutiny*, The New York Times (May 1, 2007).

problem over almost 20 years, why did the FDA wait until 2019 to request direct-hire authority for inspectors?

In May 2008, FDA was granted direct hire authority for the consumer safety officer position (0696), and approximately 800 FTEs were hired as a result of this effort agency-wide.

In April 2016, our Office of Regulatory Affairs (ORA) submitted a request for additional direct hire authority for the consumer safety officer position (0696). That request was returned with comments. We revised the direct hire request in July 2016 and September 2019 to address concerns and submitted it forward for consideration. We received direct hire authority on October 16, 2019. We are currently executing and expect hiring selection to begin in the next few weeks.

a. The hiring and retention of FDA inspectors has been a longstanding problem. Does FDA plan to commission an ontside consnltant to stndy the problem and recommend solutions and if so, when will that occur and what is the anticipated date of completion?

We have no plans to hire an outside consultant at this time.

10. Earlier this year, the Committee sent FDA a bipartisan letter asking, in part, about the FDA's India pilot program and why the program was not extended. In response, FDA told the Committee that the FDA's drug inspection initiative in India was not extended "based on a lack of protocols and evalnation criteria. No formal report or evalnation was completed." Repnblican Committee staff snbsequently asked that FDA provide information about the evaluation criteria for its foreign drug inspection program. To date, FDA has not provided this information. Does FDA have evaluation criteria for the effectiveness of its foreign drug inspection program? What are they?

FDA evaluates each inspection report prepared following each inspection regardless of program purpose to ensure that each inspection was conducted appropriately and acted on in accordance with FDA policies and procedures.

Chapter 5 of FDA's Investigations Operations Manual (IOM) includes evaluation criteria for the format and review of foreign inspection reports.[5] FDA also operates under established timeframes associated with timely completion of foreign inspection reports and issuance of any follow up decisional letters after each inspection. Additionally, the Dedicated Foreign Inspection Cadre and the GDUFA Investigators are evaluated each year to ensure that they meet either the required number of inspections conducted and/or complete the necessary weeks of foreign travel per year.

11. Your written testimony states that to help ensure that safe and effective drngs are sold in the United States, the FDA tests selected drugs in state-of-the-art FDA laboratories. What state-of-the-art FDA laboratories do this testing?

---

[5] *www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual*

FDA has laboratories throughout the U.S. CDER's laboratories are located in St. Louis, Missouri, and at the main FDA campus in Silver Spring, Maryland. ORA has medical product laboratories in Atlanta, Georgia; Cincinnati, Ohio; Detroit, Michigan; Irvine, California; Jamaica, New York; Philadelphia, Pennsylvania; and San Juan, Puerto Rico.

a. What kinds of testing are conducted?

FDA's laboratories are capable of a wide variety of testing, both chemical and microbiological. The testing we conduct on any given sample is determined on a case-by-case basis. Some types of testing are:

- Identity – is it the right drug as indicated on the label?
- Assay – how much drug is there and is it consistent with the labeled amount?
- Impurities – are there process impurities or degradation impurities?
- Dissolution – does the active ingredient dissolve out of the dosage unit so that the drug is available for the body to absorb?

b. How the drugs selected for testing?

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 reduced effectiveness. These reports come to FDA via FDA's MedWatch 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 active pharmaceutical ingredient 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.

12. Has FDA management interviewed FDA drug inspectors to get their perspectives on relying on translators provided by the firm being inspected?

No, there have not been any formal documented interviews with drug investigators to get their perspectives on relying on translators provided by the firm being inspected.

13. FDA has recently entered into mutual reliance agreements with the European Union. How will these agreements help provide more staffing and resources for FDA to focus more on higher risk foreign drug inspections?

The Mutual Recognition Agreement (MRA) between FDA and EU member states allows drug inspectors to rely on each other's factual findings from their good manufacturing practice inspections of drug facilities. The MRA reduces duplicate inspections of the same facilities and yields greater efficiencies that allow us to reallocate our resources to inspect other high-risk facilities. Developing the MRA took time and resources. Beginning in 2014, FDA experts were sent to Europe to observe EU officials audit each of the 28 EU member state (EUMS) inspectorates as part of a larger program to ensure that they could conduct inspections at a standard similar to a U.S. inspection. The FDA completed this work for the most common type of drug manufacturing inspections in July 2019.

a. How long will it take until FDA realizes these kinds of benefit from the mutual reliance agreements?

FDA and the EU have been collecting data on the operational impact of the MRA ever since the first countries were found capable on November 1, 2017, and the numbers are quite promising. With respect to CDER-regulated products, as of November 2019, the EU has conducted 29 inspections at FDA's request and FDA has conducted 14 inspections at the EU's request. Moreover, FDA has deferred 157 inspections in the EU after review of the inspectional information provided by our trusted partners. We anticipate seeing an even greater impact now that the MRA has been implemented in all 28 EU countries for human drug products.

b. How can the FDA work with friendly foreign regulatory counterparts to help improve oversight of higher risk foreign drug facilities?

In addition to FDA's collaboration with the EU member state inspectorates, we support other countries in their development of regulatory systems that are as capable as FDA's own system. We do that by collaborating in the development of inspectional policies and competency as a member of the Pharmaceutical Inspection Cooperation Scheme (or PIC/S), a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. PIC/S aims to harmonize inspection procedures worldwide by creating common standards in the field of GMPs and by providing training opportunities to inspectors. FDA has collaborated with our counterpart members to leverage inspection information, such as notifications of compliance problems and product recalls. Additionally, FDA also collaborates with industry and other regulators in establishing

harmonized guidance covering quality, safety, efficacy, and marketing application submissions. These activities and other collaborations with trusted foreign counterparts (e.g., mutual reliance on testing for the presence of nitrosamine contamination) have been helpful in supporting FDA's public health protection responsibilities.

The Honorable H. Morgan Griffith (R-VA)

1. **Has FDA considered issuing public statements to encourage drug producers to inquire about whether the API that they purchase is sourced from a manufacturer that has been inspected by FDA or another regulatory agency recognized under a Mutual Recognition Agreement? And to purchase API from facilities that have been recently been inspected?**

FDA posts inspection information on its public website that includes the name of the site inspected, date of inspection, inspection type, and the final inspection classification (indicating the severity of any objectionable inspection findings). FDA has publicly discussed the availability of this information and, in fulfillment of a GDUFA-2 commitment, updates the information every month. This data includes inspections performed by a trusted counterpart, such as EU inspectorates. FDA's regulations at 21 CFR part 211 (subpart E) require drug product manufacturers to evaluate the quality of components (i.e., active and inactive ingredients) before use in drug product manufacturing. FDA's guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, recommends that drug product manufacturers take additional efforts to evaluate their suppliers before they purchase ingredients for use in drug manufacturing, which also includes evaluating past regulator inspections.

2. **Has FDA considered publishing the investigator's establishment inspection report and any Form FDA-483 issued or regulatory action taken for foreign API manufacturers that the Agency has inspected so that API repackers and drug producers can make informed decisions about whether to purchase from those entities?**

FDA posts final FDA 483s on its website along with warning letters and untitled letters, and also announces import alert, seizure, and injunction actions. As noted in the previous response, drug product manufacturers have existing requirements to evaluate the quality of components before use in drug product manufacturing.

3. **Besides banning imports to the United States, how can FDA protect the supply chain when a foreign facility refuses an FDA inspection? When an importation ban is placed on a manufacturer, what does FDA do about API it has already introduced into the United States?**

There are a variety of advisory and enforcement actions that FDA may take when a foreign facility refuses an inspection. Import alerts allow FDA to act quickly to inform field staff of evidence that products appear to be violative, as compared to pursuing enforcement actions such as injunctions or seizures. There are steps that can be taken to strengthen the ability to use import alerts. For example, currently there are facilities that may not be subject to FDA inspection before they ship drugs to the United States. There are some firms that supply APIs that are

incorporated into products marketed in accordance with OTC monographs (and other non-application drugs), but that do not register with FDA because they do not ship directly to the U.S. As a result, some firms that produce APIs for such products are not known to FDA. Addressing these gaps in our awareness would improve our ability to use import alerts to protect the public health. FDA can request recalls for drugs manufactured in foreign or domestic facilities; however, the regulatory intervention and risk mitigation may be slow because most drug recalls are voluntary. Currently, FDA does not have the legal authority to order a mandatory drug recall other than for controlled substances when it find a reasonable probability that the controlled substance would cause serious adverse health consequences, and we only recently obtained that authority in the SUPPORT Act.

Facilities located outside the U.S. that refuse an FDA inspection may be placed on Import Alert 99-32, "Detention Without Physical Examination of Products from Firms Refusing FDA Foreign Establishment Inspection." All products exported to the U.S. by a facility on the import alert are subject to Detention Without Physical Examination (DWPE) and not released into U.S. commerce until FDA is able to inspect the facility.

FDA's application of DWPE is effective as of the date of inspection refusal. FDA does not retroactively apply the DWPE but can request recalls for drugs in the U.S. market that were previously imported and are now subject to an import alert.