PRIORITIZING PUBLIC HEALTH: THE FDA'S ROLE IN THE GENERIC DRUG MARKETPLACE

WEDNESDAY, SEPTEMBER 21, 2016

U.S. SENATE,
SUBCOMMITTEE ON AGRICULTURE, RURAL DEVELOPMENT,
FOOD AND DRUG ADMINISTRATION AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 3:02 p.m. in room SD–192, Dirksen Senate Office Building, Hon. Jerry Moran (chairman) presiding.

Present: Senators Moran, Collins, Daines, Merkley, Tester, and Udall.

OPENING STATEMENT OF SENATOR JERRY MORAN

Senator MORAN. Good afternoon, everyone. Thank you for joining us.

Senator Merkley, the ranking member, is en route and his proxy—at least he has described himself as Senator Merkley's proxy—is here and we are going to begin. I will give my opening statement and perhaps by then Senator Merkley will be here, and then we will go to testimony. The Senator from Montana has a scheduling issue, and we will try to get to him very quickly.

We are pleased to have with us today—Dr. Janet Woodcock. She is at the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research, and that agency's mission is to make certain that the public has access to safe and effective drugs.

Earlier this summer, Kansans and American families discovered that—particularly those families that had allergies, or their children had allergies, that they were faced with a dramatic increase in the cost of epinephrine injectors, or EpiPens. And in my view, that raises issues for us as appropriators for the Food and Drug Administration in this sense.

The Food and Drug Administration does not have jurisdiction over the cost or price of drugs. They are not a regulator in that regard, but their role is to make certain that drugs are effective, as well as safety. Part of that process of safety and efficacy is bringing generics to market, and I think it would be useful for our subcommittee to hear the developments at FDA in regard to that process.

I think all of us have an interest in making certain that drugs that are effective and useful are made available to consumers across the country at prices that are affordable. And one of the ways that I think we can address that is to make certain that the

process that FDA utilizes to bring generics to market is working the way it should.

And so this hearing is designed for us to elicit information from FDA, from Dr. Woodcock as to that process and what role that we should pursue as members of the appropriations subcommittee responsible for the Food and Drug Administration.

Congress approved the Generic Drug User Fee Act (GDUFA) in 2012. It was designed to address the issues that I have talked about, speeding up the process to bring generic drugs to market. In the past 3 years under this act, the FDA has collected $1 billion from generic drug manufacturers, which has translated into the hiring of an additional thousand employees at FDA and replacing, presumably, an antiquated information technology system.

Despite that, despite the thousand employees and a new computer system, there are more than 4,000 generic drug applications currently awaiting approval, and the average time it takes for FDA to approve a generic is now 47 months, nearly 4 years.

It is also my understanding that FDA is close to finalizing its negotiations with the industry on a new round of fee and regulatory requirements to address that backlog. And my guess is that Dr. Woodcock cannot speak about the details of those negotiations, but I am hoping this hearing will allow us to get a better understanding of how FDA plans to tackle that backlog and that extension of the waiting time, all in a process that still provides safety and efficacy.

On a final note, doctor, I would like to take the opportunity to acknowledge your efforts to advance the accelerated approval process for patients who have no other treatment options. And in this regard, I want to just mention particularly the Duchenne muscular dystrophy issue that has occurred at FDA, and I want to express my support for the efforts that bring that drug to market in a timely way.

[The statement follows:]

PREPARED STATEMENT OF SENATOR JERRY MORAN

This hearing will come to order.

Good afternoon. Today's hearing will focus on the Food and Drug Administration's role in the generic drug marketplace. I would like to thank Dr. Janet Woodcock for being here today. I greatly appreciate your work at the FDA's Center for Drug Evaluation and Research (CDER) whose mission is to make certain that the public has access to safe and effective drugs.

I would be remiss if I failed to note that, earlier this summer, parents of children who suffer from allergies were suddenly faced with dramatic increases for epinephrine injectors or Epipens. I have an interest in working to ensure that drugs are available to all Americans at affordable prices. The FDA's role in the drug approval process is critical to expanding the pharmaceutical market and driving down costs for consumers.

While drug pricing is not the topic of this hearing, the FDA's responsibility to approve generic drugs in a timely fashion should be part of the larger discussion on pharmaceuticals. And, Dr. Woodcock, you wrote a piece on this topic recently and it is something my colleagues may be interested in reviewing.

With regard to FDA's role in the generic drug marketplace, Congress approved the Generic Drug User Fee Act in 2012 to speed up efforts to bring generic drugs to the market. In the past 3 years under this act, the FDA has collected $1 billion from generic drug manufacturers, which has translated into hiring an additional 1,000 employees and replacing antiquated information technology systems. However, despite this influx of resources, there are more than 4,000 generic drug applications currently awaiting approval, and the median time it takes for the FDA to approve a generic is now 47 months or nearly 4 years.

It is my understanding that the FDA is close to finalizing negotiations with industry on a new round of fees and regulatory requirements to address the backlog.

And while Dr. Woodcock cannot speak to specifics of this negotiation, I am hoping that this hearing will allow us to get a better understanding on how the FDA plans to tackle the generic drug backlog and streamline the drug approval process to increase transparency, efficiency and predictability.

One final note: I would like to take this opportunity to acknowledge Dr. Woodcock's efforts to advance the accelerated approval process for patients who have no other treatment options. I know this is an issue of critical importance to patient advocacy groups, as we see with the recent approval of the first therapy for Duchenne muscular dystrophy, and I want to express my support for your efforts on that front.

I look forward to discussing these topics with our witness today. We have a lot to cover this afternoon, so I will now turn it over to Senator Merkley for any remarks he may wish to give.

Senator MORAN. I look forward to discussing these topics with you, and we look forward to my colleagues asking you questions in just a moment.

Senator Tester, we can defer to Senator Merkley when he arrives. You have a scheduling issue, and I would be glad to yield my time to you so that you could begin the questioning.

Senator TESTER. Does the doctor have a statement?

Senator MORAN. Yes.

Senator TESTER. Perfect.

Senator MORAN. Dr. Woodcock, the floor is yours.

STATEMENT OF HON. DR. JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. WOODCOCK. Thank you, Mr. Chairman and members of the committee, for this opportunity to testify.

As was already said, FDA has no role in setting drug pricing, but our actions serve to enhance competition which has been shown to decrease drug prices. For example, I would like to go through some of the actions we do take that enhance competition.

MARKETPLACE COMPETITION

We often approve multiple drugs in a therapeutic class. They are separate drugs, but for example, there are a lot of cephalosporin antibiotics out there. And so even within a class or an anti-hypertensive of a certain class, there may be a lot of drugs that compete in the market.

Also, we often approve different versions of a marketed drug once patents and exclusivity have expired that are not exact copies under our 505(b)(2) program, which is not a generic but is part of the Hatch Waxman legislation. And these copies also can compete with the marketed drug.

Under the generics program, multiple exact copies of a branded drug can be approved once all exclusivity and patents have expired. And we frequently approve several copies at once. For example, very recently we approved eight generic Crestors on the same day. So there is a first generic, but there might be eight first generics and the introduction of multiple copies into the market often can really lower the pricing of the drug.

And finally, our new biosimilars program, which was authorized by Congress a number of years ago, introduces competition for bio-

logic drugs which, of course, generally are very expensive protein drugs. And we have approved so far three biosimilars, and we have a robust program growing in the biosimilar area.

Now, I think in the generic space particularly, there have been a number of misconceptions circulating about the generics program. It is kind of easy to misunderstand the generics program.

GENERIC APPROVAL TIME

The first one is that the program takes 47 months overall to approve a generic application. Senator, you said that.

Senator MORAN. Are you telling me I am under a misunderstanding?

Dr. WOODCOCK. Well——

Senator MORAN. That is fair.

Dr. WOODCOCK. For the really old products that were in the backlog before the new GDUFA program started, the user fee program started, they already are 4 years old. And so they are not getting any younger. And as we approve them, they are going to have very long times to market because they started before that program even was put in place.

But starting October 1 of this year, if a company sends us an approvable generic drug application, we will approve it in 10 months.

Part of the problem is the generic industry does not have a high level of meeting our standards on the first try, and so they have to go through multiple cycles.

After the Prescription Drug User Fee program was put into place—now it has been 20 years—we have an extremely high rate of first cycle approvals for new drugs, which are much more complicated. So it is possible to approve drugs very rapidly if in fact the application meets our standards.

But we cannot approve substandard generic drugs because, first of all, those are our standards, but it would erode the confidence of the public in the generic drug program and really take us back to the time when generic drugs were not well accepted by the medical community.

GENERIC APPROVAL BACKLOG

Another misconception is that a lot of first generic drugs are moldering in this backlog that has been there for so long. And that is really not true. There are fewer actually than 100 applications in that backlog that manufacturers have not gotten feedback from FDA on their application.

And we had a goal of reviewing and providing deficiencies for 90 percent of the backlog by the end of the GDUFA program. That is not this coming October but next October. We already exceeded that goal 15 months ahead of schedule. So 90 percent of those backlog applications have already received communications from FDA about what their deficiencies are. And there is a large number. There are 1,700 applications, most of them from this backlog, that are with the manufacturers awaiting them returning them to the FDA with improved information. So we have really exceeded the goal that was set for us under the first user fee program by 15 months of dealing with this backlog in its first iteration.

And 500 of those that are sitting with the manufacturers have actually been there for longer than a year. And it may be that our huge activity in getting all these questions and applications back to the manufacturers for repair has somewhat overwhelmed their ability to get back to us promptly.

And there is also a belief that a large number of important generic applications are sitting untouched at the FDA, and there are almost no applications that are not touched except maybe ones that are recently submitted to us and are going through the filing process.

So it is true, however, that we are not at a steady state yet. We had built up a huge backlog, as I said in the testimony, before the Generic Drug User Fee program started, and we are still working our way through that in the sense that they will return again and again until which time they meet our standards and they can be approved. But this year alone, as you see in the slides I left at your places, we have 1,700 applications pending industry. And this year, we approved 700. In the program, we have approved 2,207 approvals and tentative approvals since the GDUFA program started. So that is the number.

PRIORITIZATION OF GENERIC APPLICATIONS

We also prioritize generic applications that may have public health implications. Sometimes we have those that are first generics that are sole source. In other words, there might be only one product out there and it is a generic. So we still prioritize the second one. And, of course, shortage of drugs, if there is a shortage, we will prioritize generic applications. We will move them to the front of the line, like the express line, to try to get them through.

I would like to say I am really proud of the work our staff has done in setting up the new generic program and the biosimilar programs. They were very tough. They required multiple changes, a very heavy lift. And I think we are showing that we are getting that work done. It has really been an enormous effort, though, on many people's part and that continues.

I am confident we will continue to improve these programs, and they will provide a pathway for competition in the market that will be very robust.

I look forward to your questions.

[The statement follows:]

PREPARED STATEMENT OF JANET WOODCOCK, M.D.

INTRODUCTION

Good morning Chairman Moran, Ranking Member Merkley, 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). Thank you for the opportunity to appear today to discuss FDA's role in executing the nation's generic drug review program. I would also like to thank the Subcommittee for its past investments in FDA, particularly the Human Drugs program. The funding, most recently provided in fiscal year 2016, has helped us meet the demands of our increasingly complex and diverse mission at home and abroad.

FDA recognizes the critical importance that generic drugs play in the U.S. healthcare system. At FDA, we recognize that when more than one version of a drug, especially when a generic version of a drug is approved, it can improve marketplace competition and help to provide additional options for consumers. Although FDA does not have a regulatory role in the pricing of drug products, we do play a

critical role in ensuring patients have access to beneficial medicines. With this role in mind, and as I discuss more fully below, FDA is working hard to support the timely, scientific and efficient development of new generic drug products for the U.S. market.

THE RISE OF GENERICS

Recognizing the need to increase the availability of low cost generic drugs, over thirty years ago, Congress enacted the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act (FDCA).The Hatch-Waxman Amendments represent a great success in facilitating the widespread availability of safe, effective and high-quality generic drugs. According to the IMS Institute for Healthcare Informatics, generic drugs now account for nearly nine out of ten prescriptions dispensed in the United States and saved the U.S. health system $1.68 trillion from 2005 to 2014.

ABBREVIATED PATHWAYS TO APPROVAL

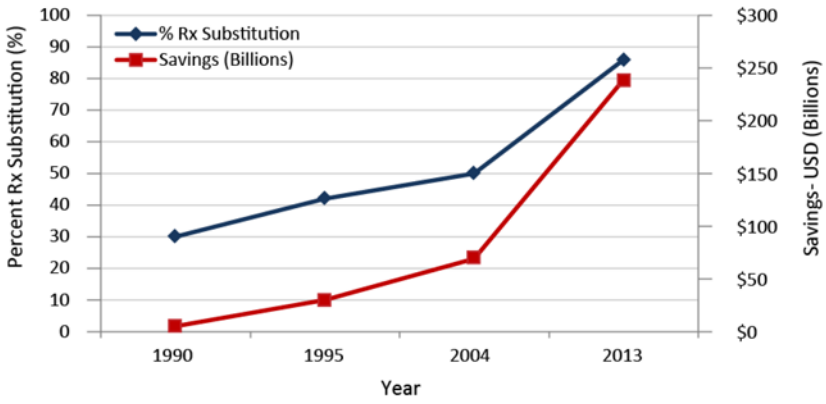
The Hatch-Waxman Amendments formally establish two abbreviated approval pathways for drug products, while at the same time provide incentives for the continuing development of innovative new drug products. One of the two abbreviated approval pathways allows for the approval of Abbreviated New Drug Applications or ANDAs. Drugs approved under this pathway are commonly referred to as generics.

Unlike an innovator drug application, a generic drug application does not need to independently establish the safety or effectiveness of the drug. Instead, the generic drug has to show that it is the same as an innovator drug in several fundamental ways, such as in active ingredient, dosage form, route of administration, strength, and labeling (except for certain permissible differences in labeling); that the generic drug is absorbed and available at the site where it will act in the body at the same rate and to the same extent as the innovator drug (which is known as bioequivalence); and that it meets the same high standards for drug quality and manufacturing as an innovator product. If the ANDA meets these requirements, the generic applicant can rely on FDA's previous finding of safety and effectiveness of the branded innovator drug, and need not conduct its own clinical investigations to establish safety or effectiveness.

FDA approval of an ANDA indicates that FDA considers the generic drug to be therapeutically equivalent to the innovator drug. This means that the Agency has concluded, among other things, that the generic and innovator drugs can be substituted with the full expectation that the generic drug will produce the same clinical effect and safety profile as the innovator product when administered under the conditions specified in the labeling. Therapeutic equivalence ratings are published by FDA in what is commonly known as the Orange Book. Although FDA does not itself determine when a pharmacy would substitute a generic drug in filling a prescription, state pharmacy laws and other regulations that determine substitutability often refer to these Orange Book ratings.

The Hatch-Waxman Amendments also established a second abbreviated pathway for drug applications. This pathway, commonly referred to as the "(b)(2) pathway," can be thought of as a hybrid between the pathway for an entirely innovative product and the ANDA pathway for a generic drug. Unlike generic drugs, products approved under the (b)(2) pathway on approval are not presumed to be therapeutically equivalent to the innovator drug and, if a (b)(2) applicant seeks a determination of therapeutic equivalence, it must demonstrate this separately.

Chart 1. Generic Substitution and Annual Savings[1]

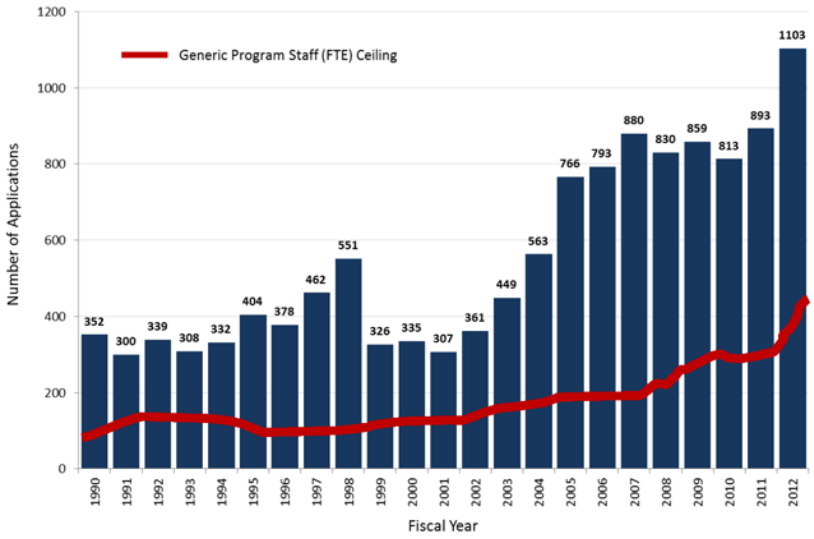


1. Annual generic utilization and savings data compiled from IMS Health, the Generic Pharmaceutical Association, and the Congressional Budget Office.

KEEPING UP WITH DEMAND

The expansion of the generic market has brought new challenges. The last several decades have seen substantial growth in the size of the generic industry, the number of ANDAs submitted to FDA for review, and the number of foreign facilities making generic drugs. As a result, FDA's generic drug program became increasingly under-resourced. Its staffing did not keep pace with the growth of the industry.

Chart 2. Number of ANDAs Submitted Per Year and Number of Staff Over Time



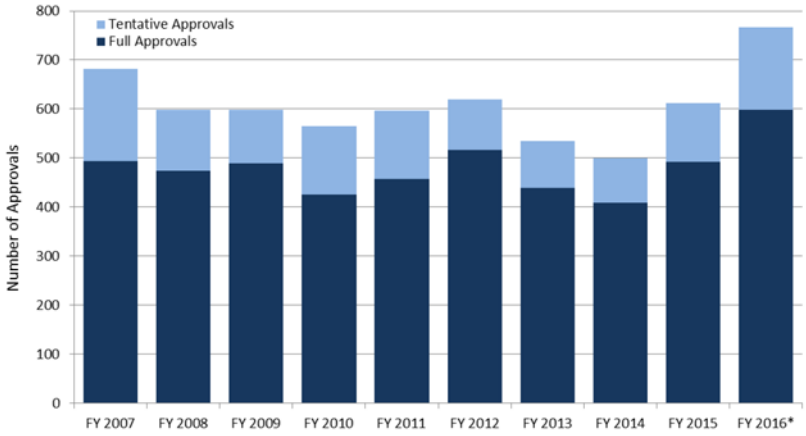
Because the program could not keep up with its workload, a backlog of submitted ANDAs developed and grew. It overwhelmed the FDA staff and created unpredictability and delay for industry.

In response to this backlog issue, Congress enacted the Generic Drug User Fee Amendments of 2012 (GDUFA I), under which industry agreed to pay user fees each year of the five-year program and FDA committed to certain performance goals.

A major commitment of GDUFA I was to take a "first action" on 90 percent of the "backlog" applications, defined as pre-GDUFA applications pending before the Agency on October 1, 2012, by the end of fiscal year 2017. As of October 1, 2012, the backlog included 2,866 ANDAs and 1,873 prior approval supplements (PASs). A "first action" on an application means granting an approval or tentative approval, or, if there are deficiencies that prevent approval, identifying those deficiencies to the applicant in a complete response letter or in a refusal to receive the application. As of July 1, 2016, FDA had taken "first actions" on 90 percent of the backlog applications, achieving this performance goal 15 months ahead of schedule. In addition, FDA has met or exceeded all performance goals under GDUFA I with respect to ANDA's submitted after GDUFA had commenced.

The cumulative result of all this effort is a huge increase in the productivity of the generics program. We ended last year at a new monthly high of 99 approvals and tentative approvals[1] in December. By July, with 2 months still remaining in this fiscal year, we had already achieved a new record of 702 approvals and tentative approvals.

Chart 3. Approvals and Tentative Approvals



*Approval numbers as of August 31, 2016

Some of the backlog applications, mentioned above, had been pending or in review for a long time prior to GDUFA. At this point in time, as FDA acts on a backlogged application, the "time to approval" of such application will be recorded as, at minimum, 47 months (i.e., we are now 3 years and eleven months (47 months) into GDUFA implementation).

Applications submitted in fiscal year 2016 have a GDUFA first-action goal date of 15 months. For fiscal year 2017, which begins in 10 days, an incoming ANDA will receive a 10 month GDUFA goal date. If the ANDA is for a priority product—such as a first generic—its review will be further expedited. This year, we have achieved a record number of ANDA approvals and a record number of first cycle approvals.

[1] Tentative approval applies if a generic drug product is otherwise ready for approval before the application may otherwise be approved because of issues related to any patents or exclusivities accorded to the reference listed drug product. In such instances, FDA issues a tentative approval letter to the applicant. FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

HOW DID FDA ACHIEVE THESE RESULTS?

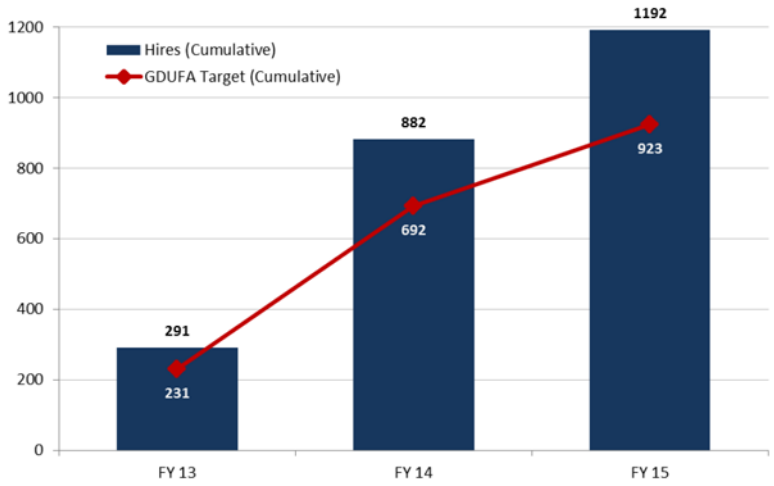
Deep, foundational restructuring

These successes were achieved by restructuring our organization for generic drug review, to build a modern generic drug program. This involved major reorganizations. We reorganized the Office of Generic Drugs and elevated it to a "Super-Office" status, on par with the Office of New Drugs. We established a new Office of Pharmaceutical Quality to integrate the quality components of the review.

We developed an integrated informatics platform to support the generic drug review process. This platform is a significant improvement over our earlier fragmented, legacy systems, and has enhanced our productivity.

We hired and trained more than 1,000 new employees, achieving our GDUFA hiring goals well ahead of schedule.

Chart 4. GDUFA Hiring Progress



FDA CREATES A PATHWAY FOR GENERICS DEVELOPMENT

In addition to the work that FDA does with individual companies to support their development of specific products, FDA also works to create a publicly available roadmap describing what companies need to do to bring various types of medical products to market.

FDA is continuing to develop, publish, and update guidance documents, which are a kind of roadmap for industry sponsors, explaining FDA's recommendations for the kind of information that should be included in a marketing application. Guidance documents can provide vital information to drug and device developers for a class of products.

FDA also recognizes that for more complex products, in addition to guidance, one-on-one advice may be needed so FDA can address technical and regulatory questions about the pathway to market. Such meetings occur now for both new drugs and generic drugs under development. In addition, FDA regularly responds to specific product-development questions from industry that FDA answers in writing to help companies develop generic drug applications through the process known as Controlled Correspondence. We hope to expand our ability to engage with generic product sponsors through a reauthorization of the Generic Drug User Fee Amendments (or GDUFA II), where complex product meetings have been described as a key provision of the proposed program.

Further, FDA prioritizes the resources we make available to focus on areas of high public health needs. For example, FDA's Office of Generic Drugs (OGD) has a prioritization and expedited review policy for certain generic drug applications. The policy is set forth in a publicly available document called a Manual of Policy

and Procedures[2] (MAPP), which can be found on the FDA website. Pursuant to OGD's prioritization policy, ANDAs for drugs that have "first filer" status or that otherwise are eligible to be the first generic approved are prioritized and given expedited review.

Each of these, and other efforts of FDA, help clarify our expectations and prioritizations concerning specific products so industry can develop and obtain approval of generic versions of branded drugs more quickly.

While FDA is working to lay out a roadmap to support efficient development of complex products, we cannot, and will not, allow a substandard product to come onto the market. In addition to working to assure the safety and efficacy of drugs, it is critical that they be manufactured to high quality standards to assure they can be used safely by patients when they are needed. FDA's new Office of Pharmaceutical Quality plays a critical role in ensuring the quality of both generic and new drugs.

FDA'S ROLE IN THE INTELLECTUAL PROPERTY LANDSCAPE

Although FDA can and does encourage generic drug development and has and continues to streamline and improve its review and approval of generic drug applications, the decisions of whether to seek approval for a proposed generic drug and whether to market an approved generic drug are controlled by the generic drug industry. Further, the extent to which the approval or marketing of generic drugs is delayed because of intellectual property rights or marketing exclusivities is largely controlled by the innovator-drug manufacturers and others that hold those rights.

With respect to patents, FDA has only a "ministerial" role. As noted earlier, the Hatch-Waxman Amendments sought to balance two competing goals: (1) increasing the availability of generic drugs, and (2) increasing incentives to develop new and innovative drug products. In addition to creating certain marketing exclusivities, the Hatch-Waxman Amendments established a set of procedures intended to align the generic drug approval process with an opportunity for the owners of innovator drugs to assert certain rights for patents covering the innovator drug before generic drug approval. While FDA plays a role in this process, our role is very limited.

First, sponsors of innovator drugs must submit to FDA information regarding certain patents related to their products. FDA lists these patents in the Orange Book. In any application that seeks to rely on a previously approved NDA, which includes (b)(2) applications and generic drug applications, the applicant must describe whether it intends to challenge those listed patents in court. Specifically, the applicant may inform FDA that there are no patents listed, or that the applicant is not seeking approval until after a patent listed in the Orange Book expires. Alternatively, an applicant can also notify FDA that it intends to challenge a listed patent as invalid, unenforceable or not infringed. Where an applicant seeks to challenge a patent, the applicant is required to submit to FDA certain information regarding its patent challenge and any resulting patent litigation as part of its application; but, the challenge and litigation take place between the applicant and the patent holder(s) in the courts and outside FDA's regulatory authority. If an applicant is challenging a patent, the law describes when FDA can approve the application in a complex scheme, including a potential 30-month stay of an approval if the ANDA applicant is sued soon after making the patent challenge. In each case, the ANDA applicant's decision regarding whether to challenge a patent, and when applicable, the innovator sponsor's response, and the court's decision on the patent can affect when FDA may (and may not) approve the generic drug application.

As drug applicants often publicly acknowledge, they routinely take the intellectual property rights of previously approved drugs into account when making determinations regarding the design and development of their proposed drugs. While our approval standards are the same whether or not an applicant designs its proposed product around a competitor's intellectual property rights, the proposed products that FDA receives for review and consideration for approval are no doubt impacted by patent considerations.

OVERVIEW OF THE EPINEPHRINE AUTO-INJECTOR MARKET

Epinephrine auto-injectors, with the most widely used and recognizable product being Mylan's EpiPen, are a critically important, and potentially life-saving, product for patients who suffer from a severe allergic reaction called anaphylaxis. These products are considered combination products since they consist of a drug component (epinephrine) and a device component (auto injector). When a patient requires

[2] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf

the medication, seconds count, and the epinephrine auto-injector must work every single time. To ensure this, it is critical that both the drug, and the device that delivers the drug, perform as designed.

At FDA, we are aware of the recent spike in the price of the EpiPen. FDA has approved four epinephrine auto-injector products to treat anaphylaxis; two of which are currently on the market. While there are currently no FDA-approved generic epinephrine auto-injectors, we stand ready to quickly review additional applications that come to us from both generic and innovator drug companies.

Mylan's EpiPen is the market leader for epinephrine auto-injectors in the United States, and Mylan has recently publicly announced they also will offer an authorized generic version[3] to be available in the near future. Another firm, Amedra holds an approval for Adrenaclick, which is also an epinephrine auto-injector. Currently, while the Adrenaclick brand name product is not being marketed, Amedra is marketing its own authorized generic version of the drug. Amedra also previously marketed Twinject, but this product has been discontinued. Finally, FDA also approved Auvi-Q as an epinephrine auto-injector, although this product was voluntarily recalled from the market in 2015 by Sanofi. We note that Auvi-Q was recently purchased by Kaleo, though this product has not yet returned to the market. In support of increasing the number of epinephrine auto-injector products on the market, FDA is committed to working with both Amedra and Kaleo to facilitate greater availability of their products.

CONCLUSION

Thank you for your interest in the important topic. FDA takes seriously its role in executing the nation's generic drug program, and we understand the importance of generic products in the U.S. marketplace. We anticipate that our ongoing efforts to continue to improve generic drug development will provide dividends in both protecting the health of Americans as well as in cost savings long into the future. We hope that our efforts, coupled with the work of other groups that also have roles to play, will continue to ensure medications are readily available to patients. I am happy to answer any questions.

Senator MORAN. Doctor, thank you very much.

Let me now turn to the ranking member, Senator Merkley, for any opening statement you would like to make.

STATEMENT OF SENATOR JEFF MERKLEY

Senator MERKLEY. Thank you very much, Chairman Moran.

I think there is a lot of interest in this hearing and the role of generic drugs and the role that they can play in diminishing drug prices in America, which are a significant factor in the overall costs of our health care system and certainly a significant factor for families that have deductibles, as so many working families do have.

We have had a series of cases where a drug company controls a single product in a particular segment of the medical market, a single drug or has a large share of the market, putting them up for sale at vastly increased prices, very sudden, very dramatic price increases. It seems like about every month there is some prominent story that catches the attention of America. The most recent of those is the EpiPen and the Mylan company, the dramatic increase from roughly $100 to $600 for a pack of two, despite the fact that the drug within them, I understand, costs very little in terms of what is inside those injectors.

So as we ponder all of these cases, we are very interested in the approval process. There are other dimensions of this as well. Such as a challenge when companies buy up generics in order to keep

[3] An "authorized generic" is made under the brand name's existing new drug application using the formulation, process, and manufacturing facilities approved for use by the brand name manufacturer. The labeling is changed to remove the brand name or other trade dress. An authorized generic is not synonymous with an FDA-approved generic, the latter of which requires a separate application and approval from that of the brand name product.

them off the market or use patent changes to try to keep them off the market or pay generic companies to keep them off the market, market manipulations of this kind. These may not be things that you are able to be part of in your role of looking at the effectiveness and reliability of drugs, but they are part of the broader picture that is of great concern to Americans.

So I look forward to hearing my colleagues and hearing from you and exploring this because there is a lot of room for improvement. Thank you.

Senator MORAN. Senator Merkley, thank you very much.

I would yield my time to the Senator from Montana.

GENERIC DRUG PRICE INCREASES

Senator TESTER. You are very kind, Mr. Chairman. I thank you for the courtesy.

And you are right. This is a very, important issue. As I go home, I hear from not only patients and friends and family, but I hear from doctors about what is going on with pharmaceuticals. Even though my questions do ultimately end up applying to money, it deals really with your job, and the ranking member talked about this briefly.

But can you tell me how a company can take a generic and change it very, very slightly and end up to be able to go take it back on the market and jack the price up when it is basically the same generic it was before they modified it very, very modestly? Talk to me about how that process works.

Dr. WOODCOCK. Certainly. The generics have to be copies of a reference listed drug, in other words, a brand drug originally.

Senator TESTER. Yes.

Dr. WOODCOCK. And so they have to stay being copies. So they cannot substantively modify the generic. They may make it look different or something like that, but in our experience, the price rises for generics or innovative products, as you were referring to, have to do with no competition in the market, where they may be the only game in town. Overall, generic drug prices are going down, and have been going down. But in these cases that you are referring to where, for some reason, there is no competition, there may be other approved generics, but as Senator Merkley said, their market share may be so small or for other reasons that there is not effective competition.

Senator TESTER. Well, I will tell you I appreciate that. And I do not have any problem with a pharmaceutical company getting their research and development money back. I also think that if we are funding part of that R&D, we ought to get a break on some of that R&D money. But that aside, I think it is important they are able to do their research.

But I have heard from many docs—not just one or two, many docs—that say that if a patient is using a generic, the company will pull that back, somebody pulls it back, changes it not significantly at all, and then puts is back on the market for 5 or 10 times the money or more.

Dr. WOODCOCK. What you may be referring to is the ownership changes. So one generic company may own a product. It is then sold so that it looks different. It has a different manufacturer.

Senator TESTER. But it is the same stuff basically.

Dr. WOODCOCK. It has to be under the generic laws.

Senator TESTER. Is there anything we can do about that, or is that just the way it is?

Dr. WOODCOCK. FDA, as I said earlier, does not regulate the prices of drugs. We have nothing to do about that.

Senator TESTER. Okay.

Dr. WOODCOCK. What our actions do is we try to, if there is a sole source, we try to get more copies into the market.

BIOSIMILARS

Senator TESTER. I have got a friend who was diagnosed with child diabetes at the age of 13. He is the same age I am. He is 60. So this is 1970 when he first became a diabetic. And I cannot remember the number because it has been over a month ago, and my memory does not last that long. But he had told me that insulin back in 1970 was less than $10, and now it is significantly much, much higher than that. Has insulin changed over the last 40 years, or is insulin insulin?

Dr. WOODCOCK. There are many new forms of insulin that have been introduced, and modern diabetic care usually includes a long-acting insulin and some short-acting insulins. There are insulin pens that people can auto-inject so it is less painful. So there have been different changes in technology, but some of the basic insulins have not changed.

Senator TESTER. I mean, is it just pure greed that they would increase the prices like that?

Dr. WOODCOCK. Well, I cannot comment on the motives, but I can say that Congress passed a number of years ago legislation for biosimilars so that the biologic products—would have additional competition.

Senator TESTER. Yes.

Dr. WOODCOCK. Now, insulin right now is regulated as a drug. This is complicated. But it will be regulated as a biologic. Under the biosimilars act, it will transition over. And therefore, the insulins will be subject to the biosimilars copies.

Senator TESTER. Well, I appreciate your testimony today. I am going to have to get the companies in and visit with them to find out what is going on. Like I say, I get it. You got to recoup your cost of research and development, but man, oh, man, I am just hearing so many stories on the street where there are minor modifications on a drug that is really the same drug that has been around for 45 or 50 years and is getting priced out of the marketplace, and we are driving people into poverty in the process. And quite frankly, that concerns me.

Thank you very much, and thank you for your courtesy, Mr. Chairman.

Senator MORAN. Thank you, Senator Tester.

EPINEPHRINE AUTO INJECTORS

There is no doubt but what the cost and price of drugs is an important public policy issue. It has significant consequences to Kansas families. It has significant consequences to taxpayers as we look at Medicare costs. And I hope our focus in this hearing will

continue to be how do we make certain that FDA is doing its job well to create competition and opportunities for families to make other choices and to hold down the cost, those prices of those drugs as a result.

Let me ask a couple of questions. First of all, EpiPen in particular is a combo. It is a combination between a device and a drug. Are there unique circumstances that make the generic to be more difficult in that circumstance because of the combination?

Dr. WOODCOCK. Yes. The firm that markets EpiPen has patents on the device component that go through 2025. So any firm wishing to make a generic would have to be able to get around those patents somehow and not infringe upon those patents or challenge them successfully to market a copy.

Senator MORAN. I think your column talks about generics for the drug, but they are not widely used.

Dr. WOODCOCK. This is confusing too. There is another brand of epinephrine auto-injector that FDA has approved. We have approved a number of them, but they are in the first category I talked about. They are all standalone new drug applications. So they are not generic copies. They are each one separate. Each of them does the same thing. It treats anaphylaxis, though.

There is something that people call an authorized generic. It is very confusing because it is not a generic. It is when a brand name company decides to market their product, usually along with marketing their brand product, they take the brand name off of the label and they make it look like a generic and then they market that, usually at a lower price. And so some people have the brand loyalty who stay with the brand, but then they can also compete in the generic market with the authorized genric version. It is the same product. They make it in the same plants usually and everything. It just has a different label on it.

And so the other manufacturer of the current epinephrine auto-injector, which is not called "EpiPen," it is Adrenaclick—that one has an authorized generic, and that is what is currently being marketed.

Senator MORAN. Thank you, I think, for that clarification.

[Laughter.]

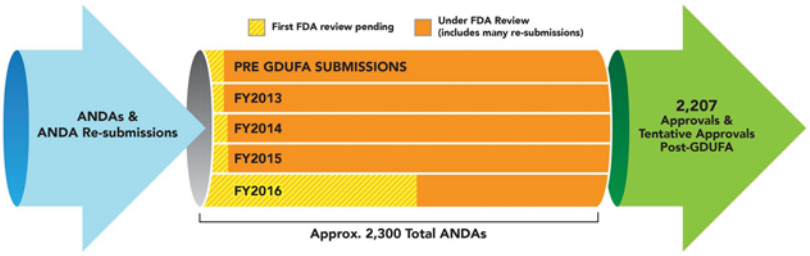
Dr. WOODCOCK. Sorry.

GENERIC DRUG APPROVAL BACKLOG

Senator MORAN. First of all, let me ask this question. I indicated in my opening statement about a backlog. You did a pretty persuasive set of statements that indicate that there really is not a backlog. And so if we were asking you what are you going to do to solve the backlog problem, you would tell us that the FDA is on path in the way that it should be. Is that fair?

Dr. WOODCOCK. At the very back of the papers I passed out, there is this chart, and what it shows is right now there are 2,300 abbreviated new drug applications (ANDAs), which is the generic drug applications, in the process of FDA reviewing them. The pre-GDUFA ones are here at the top. They were the backlog. Now they have come back in. We are reviewing them again, not all of them. And then each year, the goals become shorter for us to do the first review. And as I said, next year, 2017, it is going to be 10 months.

So to be honest and completely straightforward about this, these are more applications than we would like to have in process. It would be better if we had fewer applications in process.



Dr. WOODCOCK. I have given authorization to our manufacturing reviewers to hire 50 more people, temporary people, who are going to work on trying to get this down. But mainly this is going to be up to the manufacturers to submit to us approvable applications, and then we will be able in a cycle to approve them. If they still have deficiencies, then they have to go back and it takes longer.

Senator MORAN. The way, Doctor, that I understood your testimony is that what I described as a backlog really is applications that are pending that have been reviewed to some extent but not yet approved, sent back to the drug manufacturer for further actions on their part.

Dr. WOODCOCK. That is correct. There are about 1,700 with the manufacturers.

Senator MORAN. And are those problems with the application—are they process in the proverbial sense? They did not cross the T and dot the I? Or these are substantive issues, did not provide the necessary justification for an FDA decision?

Dr. WOODCOCK. We have tried to make these all substantive. Part of the changes we made for GDUFA was that we are calling the people all the time while reviewing their application—we call that information requests—so that these minor issues do not delay a decision on an application. And so we are back and forth. We send out thousands of these information requests and try to get the application fixed up as much as possible. But then when we send it out as a complete response, then the manufacturer has substantive work to do.

Senator MORAN. I have a series of other questions, but let me turn now to Senator Merkley.

EPINEPHRINE AUTO-INJECTOR PATENTS

Senator MERKLEY. Well, thank you very much, Mr. Chair.

You mentioned, Dr. Woodcock, that there is a competitor. I believe the name is Adrenaclick.

Dr. WOODCOCK. Yes.

Senator MERKLEY. So that competitor also has an injectable device.

Dr. WOODCOCK. Yes.

Senator MERKLEY. But you also mentioned that anyone who wishes to compete has to get around the patents that EpiPen or Mylan has. What is the difference in these two products, and how much of a barrier are those patents? And does Adrenaclick also have its own set of patents so the world of figuring out how to easily inject something is now wrapped up by these two companies?

Dr. WOODCOCK. Well, we actually have approved over the years five different epinephrine auto-injectors. Three of them are not on the market right now. I do not know what Adrenaclick's patents might look like. We can get back to you on that. We do not know.

[The information follows:]

Adrenaclick was approved on November 25, 2009 as a supplement to the Twinject NDA. The manufacturer of Adrenaclick has chosen to market Adrenaclick without a trade name, i.e., as an 'authorized generic' for Adrenaclick. An "authorized generic" is made under the brand name's existing NDA using the formulation, process, and manufacturing facilities approved for use by the brand name manufacturer. The labeling is changed to remove the brand name or other trade dress.

The Orange Book does not currently list any patents for Adrenaclick.

Dr. WOODCOCK. But that does not mean copies cannot be made. It simply means that because of the intellectual property rights, that they would either have to be challenged or an auto-injector would have to be made that performed similarly but did not use the technology.

Senator MERKLEY. Precisely. But it sounds like you are saying there have been five different approaches that have all been approved at different points in time.

Dr. WOODCOCK. None of them generics. Correct.

Senator MERKLEY. So Adrenaclick has one of the authorized generics that you referred to, a version of itself, I gather. And EpiPen is planning to do so.

EPINEPHRINE DRUG PRICING

What is the cost of the actual amount of epinephrine that is in one of these pens?

Dr. WOODCOCK. The cost of the epinephrine is probably insignificant. There is a cost, obviously. It is a chemical. But it has been around for 100 years.

Senator MERKLEY. So I have been told it is probably about $1. Does that sound feasible?

Dr. WOODCOCK. That would be probably a generous estimate.

Senator MERKLEY. So if I am somebody at risk for this challenge of my throat closing down and I am unable to breathe, then I would suffocate, can I legally acquire a little amount of the drug and put it into a syringe and inject myself?

Dr. WOODCOCK. Yes. A doctor can write a prescription for you to have that available for you. I myself personally have treated patients because I ran an allergy clinic for a while, and I did not have

an auto-injector. I injected them with epinephrine. The problem is if you are suffering an acute reaction and you are sick——

Senator MERKLEY. You want to move fast.

Dr. WOODCOCK. [continuing]. You got to move fast. And if you do not do this all the time, it is not something that is intuitive. So it is not as good as using an auto-injector.

EPINEPHRINE MARKETPLACE COMPETITION

Senator MERKLEY. So I am challenged to understand why competition does not kick in more quickly. If someone out in our audience today said, there are three other companies that have approved auto-injectors, I will go to one of them, I will rent their technology, I will get a pen up on the market that will cost—instead of $600 for two pens, I will sell it for $200. I will make a ton of money. Why does that not happen? Is your agency so difficult to deal with that it is just a huge inhibiting factor to people who would ordinarily see an opportunity?

Dr. WOODCOCK. Well, according to my staff here, we have approved four auto-injectors. So we cannot be too difficult. Not five but four. We cannot be too difficult to deal with.

It is harder, though, to get a generic copy approved because of the patents that have to be——

Senator MERKLEY. Right, but you said these others are no longer on the market. So somebody could conceivably make a purchase, license, rent the patent, pay a payment for the patent. And it is not happening. And yet, there is this vast amount of money being made.

What is the barrier for entrepreneurs stepping into this gap? It just seems like it is a dysfunctional market. Let us say someone here wanted to do this. Would they have to go through an approval process through you from scratch even though the pen has already been approved?

Dr. WOODCOCK. No. Companies frequently, as we were discussing earlier sell their rights to something to someone else, including the new drug application can be sold, and then picked up by someone else. They can reintroduce the product. They have to show us their manufacturing and so forth then, but they do not have to go through again showing safety and effectiveness.

Senator MERKLEY. So when you ask yourself the question why has somebody not jumped into this gap, is it because in getting their manufacturing approved that that is so difficult that although there are bazillions of dollars to be made, they just think it is an unworkable process? What is this huge barrier to market entry when there are available patents out there that are not being utilized for an auto-injector?

Dr. WOODCOCK. I do not know. We have approved—as I said, since GDUFA started, we have approved 2,207 approvals or tentative approvals for generics. So clearly, the barrier is not insuperable for many companies to get generics onto the market.

Senator MERKLEY. I am hoping somebody with an entrepreneurial spirit will jump in here tomorrow and figure out how to create some competition here. We would like to see a generic certainly, but as you pointed out, these are pathways given other auto-injectors have been approved.

My time is up. I am going to defer to my colleagues. But something is fundamentally difficult that is preventing ordinary investments and market entry from occurring, and I think we have to understand that better.

Senator MORAN. The Senator from Maine, Senator Collins.

AUTHORIZED GENERICS

Senator COLLINS. Thank you, Mr. Chairman.

Good to see you, Dr. Woodcock.

I know that you are very familiar with the investigation that the Aging Committee under my leadership and Senator McCaskill's leadership has conducted into the pricing of certain prescription drugs.

I want to follow up on your comments about Mylan's decision to introduce what is called an authorized generic of the EpiPen. I have to say that strikes me as gaming the system. Essentially what Mylan is doing, as you confirmed, is just changing the label on its product and then selling it for a lower price. But does that not have the effect of reducing the incentive for a true first generic to come onto the market?

I know that you have approved others and that some have been recalled due to problems.

But in general, the idea of a brand name company simply swapping the label on its product and then issuing it as a generic strikes me as greatly reducing the incentive for a true first generic to come on the market. Could you comment?

Dr. WOODCOCK. I am no economist, but I would say that would depend on how much a generic company felt they could make in the market based on what they could price their generic at.

In the Food and Drug Administration Safety and Innovation Act (FDASIA), I believe Congress asked us to require companies to tell us if they are making an authorized generic in their annual report and for us to post that information. And so far, we have noted 980 authorized generics that we have been notified about of different drugs. So it appears to be a relatively common practice in the industry.

Senator COLLINS. And I think it is one, personally, that does need more examination as far as its impact on discouraging a true first generic or second generic to come onto the market.

Let me switch to a different issue that came up in the course of our investigation, and that is, we found that certain drug companies were putting their brand name drugs into restricted distribution systems. And that made it difficult, according to our investigation, for generic companies to get a sufficient amount of the drug in order to conduct the bioequivalence studies that FDA requires.

What can be done about that?

Dr. WOODCOCK. Well, we agree. We have received over 100 inquiries from generic companies about problems they have been having in getting enough of the reference listed drug. In some cases, this relates to REMS that we have, a restricted program for safety. However, we have tried to remedy that by writing a letter to the reference company saying use of the product for this purpose is acceptable and it does not violate the REMS. Nevertheless, companies even have their own restricted distributions outside of

REMS, as well as the REMS, and clearly this is impeding the ability to obtain enough drug to compare.

With respect to what could be done about it by Congress, we remain concerned that many of these drugs are so valuable that companies will do a great deal to delay generic competition. It is worthwhile. So any type of legislation that would have a lot of extra steps and so each one of those would be an opportunity to sue us or send us a citizen petition or say we did not do the process right or whatever and get into court and delay introduction of the generic or delay availability of that product. So I think in considering what you might do about this, you have to consider—fines and everything might simply be considered a cost of doing business because there is so much at stake in delaying generic competition.

Senator COLLINS. I think this is another real problem because the system is not supposed to work that way. The REMS system is, as you said, safety-oriented. It is not intended to restrict distribution in a way that prevents the generic company from gaining access to a sufficient quantity of the drug so that they can do the bioequivalence studies.

So I hope you will work with us to try to come up with something that does not have the kinds of unintended consequences that you said and yet prevents companies—and we found all sorts of examples of this and other means that companies were using to try to block or delay the introduction of generics.

Thank you.

Senator MORAN. Senator Collins, thank you very much. And I know that your committee with your leadership has a significant interest in this topic, and I appreciate your presence today.

The Senator from New Mexico, Senator Udall.

RISING DRUG PRICES

Senator UDALL. Thank you, Chairman Moran and Ranking Member Merkley.

Dr. Woodcock, it seems like every few months, we hear about another pharmaceutical company raising the cost of a certain drug or device to a new astronomical price. The EpiPen auto-injector is the most recent to draw national attention. The EpiPen has become so expensive that families in my home State of New Mexico and across the country are struggling to afford it, even though their doctors say they must carry it in the event of an allergic reaction. But Mylan, the manufacturer, has increased the price of the EpiPens in the United States by over 480 percent since 2009.

And I have received messages from many of my constituents in New Mexico who are directly impacted. I have heard from worried parents across the State, one of them like a woman name Paige Vest from Truth or Consequences, New Mexico. Her daughter suffers from a severe peanut and tree nut allergy. She needs to carry an EpiPen with her at all times to prevent a possible life-threatening reaction. Paige wrote to me about her family's struggles to pay for the medication. She even had to change jobs in order to get insurance that would help cover the cost, you know, change jobs in order to get the medication for her child.

And I am also worried about the impact these price increases will have on families who can no longer afford the EpiPen. Linda

Thompson from El Prado, New Mexico, wrote to me that because of rising costs in recent years, she has stopped buying and carrying an EpiPen. She is forced to go against the advice of her doctor who prescribed the EpiPen after a severe reaction to a bee sting. So no one should have to go without a medically necessary product because of how much it costs.

And that is why I wrote to Commissioner Califf last week, along with members of the New Mexico congressional delegation, requesting that the FDA utilize all available resources to build a robust pipeline of EpiPen alternatives.

You know, listening to those constituents, I would like you to answer for them because I think the real question they have of you and the FDA is how did we get to this point. What happened to create this situation, how we got into a monopoly situation that we are talking about? And could you just describe that as simply as possible how you think we got here? And is it not terribly troubling that this company now is further trying to encroach into the market because they are apparently going to put out a generic. So they are trying to keep the market to themselves. They have their own EpiPen that is brand named, but then they are going to put a generic out on the market. So could you try to answer that as simply as possible? How did we get here?

Dr. WOODCOCK. Well, for most drugs, once they lose their patent protection and so they can have generics, most drugs do get generics. But some drugs do not. Either they have patents that—in this one, the EpiPen has patents that go through 2025. And so it is not easy to make a generic that does not infringe upon those patents and still works.

In other cases, it might be a small market—I am talking about for other patients in New Mexico who have seen price rises—or a single source drug. In other words, only one company sells it.

And so in all these cases, they do not have competition. And in the United States, that is what keeps prices down, is competition. So for many of these situations, when we have looked, there is some reason that competitors have not effectively entered the market and brought the prices down.

EPIPEN MARKETPLACE COMPETITION

Senator UDALL. And what is causing that? Because you said you have approved four of these, and yet, as Senator Merkley asked, why is somebody not stepping up and saying, you know, there is a lot of money to be made here? Who do you point to to say what has caused this monopoly situation that has these astronomical prices?

Dr. WOODCOCK. Well, there is one other competitor to the EpiPen on the market.

Senator UDALL. Yes, this Adrenaclick.

Dr. WOODCOCK. Yes. Several others were pulled off. One was pulled off for performance problems. For a drug like this in a situation like this, you want it to work. So you do not want to say, well, FDA should rush something through even though it might not work all the time because if that were your life that were at stake, you would want it to work every time. So we have to make sure that if there is competition here that it still works as an epineph-

rine auto-injector, and it is going to deliver the lifesaving medication when we have a life-threatening anaphylaxis happening.

Senator UDALL. Mr. Chairman, just to wrap up, you mentioned the patents over and over again that seem to be part of this. And I know it is not in the jurisdiction of this committee, but I think that is something we really should be looking at, is what the patents are doing to create monopoly situations.

But we appreciate your service and thank you very much for being here today with us.

Senator MORAN. I thank the Senator from New Mexico.

I now recognize the Senator from Montana.

DRUG PRICE INCREASES

Senator DAINES. Thank you, Mr. Chairman, Ranking Member Merkley.

Dr. Woodcock, thank you for coming here today.

And we are here today because of huge spikes in the prices of some specific prescription medications. And I share Senator Udall's concerns, what he is seeing in New Mexico where we have seen a 400-percent increase in the price of that EpiPen. That has kind of been the poster child of late here as it relates to what is going on in pricing. It is a lifesaving drug. It is a delivery system that not only people in New Mexico rely on, people in Montana and all across the Nation.

Without the competition, of course, on the market, these spikes will go unchecked. I am greatly concerned about the impact on Montanans, some of whom have to choose between buying their prescription drugs and buying food. We need to increase competition, as you have already mentioned, creating market checks on the price of drugs and decreasing costs for those who need them.

ENHANCING GENERIC DRUG COMPETITION

In your testimony, you highlight the savings that generic drugs afford, saving some $1.68 trillion over the past 10 years. In Montana, that has translated to $682 million saved in 2014. For example, according to the Generic Pharmaceutical Association's forthcoming generic drug savings in the United States report, Lipitor, a common cholesterol drug—it was $3.29 a pill before the generic was introduced in 2011. That generic now sells for 14 cents a pill, a 96-percent savings.

So my question is, what are the FDA and the Office of Generic Drugs doing to incentivize the production of more generics, particularly when there is little or no competition while maintaining, of course, drug quality and drug safety?

Dr. WOODCOCK. Well, what we do is, number one, we expedite applications where there is no competition. So if it is a first generic, if there is just a brand, we expedite that competition. And as I said, often nowadays with the modern program we have, we will approve multiple copies at once because that often will drive the price down more than a single copy. If there is just one generic, and the reference drug has been withdrawn, so we have a sole source situation, then we will expedite that as well—that application or multiple applications because we do not know which one is going to actually get approved.

Senator DAINES. So kind of going along that line of thinking, reducing the barriers to generics entering the market would clearly help create other examples like Lipitor by reducing the turbulence we see in the market and decreasing costs. The FDA has proposed a rule to modify labeling requirements for generics, but there are significant concerns that this would prevent some generics from actually getting to market. Since you have delayed the publication of the final rule now until next year, what revisions are you considering to help bring generics to the market?

Dr. WOODCOCK. Well, this rule is not about helping to bring generics to the market. We got a lot of comments on the rule. We had a public meeting after the proposed rule was published, and we have received a large number of comments from the stakeholders and we are still evaluating those comments.

GENERIC DRUG USE FEE PERFORMANCE GOALS

Senator DAINES. In looking at what do you mean by turbulence in terms of a concrete example, it was brought to my attention that there are certain applications now being assigned what they call target goal dates instead of target action dates. As you know, a goal date is not binding, giving little clarity to the applicant. What are you doing to address those concerns?

Dr. WOODCOCK. Well, under the agreement we made under the Generic Drug User Fee Act, we agreed to have goals for 2014, 2015, and 2016. And so in 2016, there will be a goal of 10 months, and if someone sends in October 1 of this year, if they send in an approvable application, it can be reviewed and responded to and on the market in 10 months.

Senator DAINES. But a goal date is not binding.

Dr. WOODCOCK. Well, sometimes there are other factors that come in. We have goals. Our goal is we would do 90 percent of them within the 10 months. That is how our PDUFA program works too, Prescription Drug User Fee program.

Senator DAINES. So do you think by shifting more to these goal dates versus action dates, it would actually speed up the process and create more certainty?

Dr. WOODCOCK. The earlier dates, the target action dates, were for the backlog that did not have any goals associated with it. Our agreement under that was we would take an action on 90 percent of those by the end of the 5 years, and we already did that. So we exceeded that by 15 months. We have acted on almost all of those.

Senator DAINES. My time is up, Dr. Woodcock.

Just to conclude, I understand there is currently more than 14,000 approved generics, and I believe that incentivizing new, safe, and effective generics and promoting competition is very important for Montanans and all Americans.

So thank you for your thoughtful comments. I encourage you to facilitate this by reducing these barriers to entry and by providing stability for manufacturers to be able to plan effectively and to continue to bring safe and quality generic drugs to market. Clearly, we have seen a lot of great successes there.

Thanks, Dr. Woodcock.

Senator MORAN. Thank you, Senator.

Doctor, you indicated earlier that you have the ability to prioritize within the backlog, and you listed a few criteria by which you might prioritize. You indicated in your comments to my colleague, the ranking member, you used the word "only game in town." What you mean is little or no competition. Is that a criteria by which you can prioritize from that backlog?

Dr. WOODCOCK. Yes.

Senator MORAN. And you do that?

Dr. WOODCOCK. Yes, and it is not just the backlog because there really are not so many in there. Even an application we would get today or tomorrow or October 1, we would still try to prioritize that if it were a single source, like if there was only one drug on the market.

Senator MORAN. Okay.

And you indicated in your testimony and in part in response to my questions that often substance within the application process, substance within that application is insufficient for an approval, and therefore that application is still pending and would be considered in my words part of the backlog. But it is really waiting on then the applicant to do something more to make that application more viable and potentially approvable. Is that a summary of what we are talking about?

Dr. WOODCOCK. Yes.

Senator MORAN. And you indicated to me, which I was pleased to hear, that this is not about crossing the T's and dotting the I's. This is substantive issues as far as whether the drug application should be approved. And then again, you indicated that you let the drug companies know throughout the process where there might be problems. They have the opportunity then to correct those issues as the application is going through the process.

Dr. WOODCOCK. That is correct.

Senator MORAN. Is that still true?

Dr. WOODCOCK. That is correct.

Senator MORAN. And so it is not like starting over at the end. So you do not deny an application and say to the drug company, I am sorry you do not qualify, you do not get our approval, go fix something, and come back and apply again.

Dr. WOODCOCK. No. What we do is send what is called a complete response. We do not send out denials. We send out a complete response. It says these are the things you must do before your application can be considered approvable. And that has to include the facilities. And often an application may have, say, 14 facilities around the world that they are relying upon, say, for testing this part of the manufacturing, this part of the packaging. We have to make sure all those facilities are in good standing. And so perhaps they may have to work on improving a facility—it might be in another country—or switching to a different facility. And these are the kind of problems they face sometimes.

Senator MORAN. Does that approval process involve inspection of a facility?

Dr. WOODCOCK. Yes.

Senator MORAN. Or this is a paper process?

Dr. WOODCOCK. There are a large number of facilities around the world that make drugs, generic drugs, for the United States or test the drugs or do the bioequivalence testing. So we try to have a schedule for inspecting those and inspecting them every several years on a regular basis. But sometimes there will be new facilities that will come in with the application or they will be doing something they never did before, like they will be making a sterile product, which is very different than making a tablet. And so we would go and inspect them as well. So sometimes if they have had a fairly recent inspection and are in good standing, we will not inspect them again.

Senator MORAN. Is there a common denominator for drug companies who are required to submit additional information during the approval process? Those that are in a, quote, backlog—is that a smaller company as compared to a larger company, someone who is new to the market, a new entrant to the pharmaceutical business?

Dr. WOODCOCK. We wish. I mean, we have tried to discern this and what is causing this problem because before the Generic Drug User Fee program, almost no generic drugs were approved on the first cycle. They were all deficient. And often they went through four cycles. I think that was the median. So there was a tremendous amount of work and kind re-picking it up and looking at the application again, and it was a long period of time. Of course, many of them could submit before the patents expired, so they had some time to work on their application.

So we are trying to do a lot of analysis to answer your question because we want to know that too. How can we remedy this situation?

In PDUFA, the new drug side, the prescription Drug User Fee Act, we are way up to 85–90 percent first cycle approvals. So over the 20 years of that program, we have taught the industry what they need to do to send in an approvable application. And we meet with them before and so forth so that we can get through the application efficiently.

Senator MORAN. I will follow up on that as soon as I turn to Senator Merkley and he has concluded his questioning.

ANTICOMPETITIVE PRACTICES

Senator MERKLEY. So the competitor that was taken off the market—I believe it was Auvi-Q—came off at their own decision—they were not forced off—roughly a year ago. Do we know if Mylan is paying them to keep that product off the market?

Dr. WOODCOCK. I do not know anything about those business arrangements.

Senator MERKLEY. Would that be legally allowed under the law?

Dr. WOODCOCK. You know, what we do is refer these type of things to the Federal Trade Commission. You know, we get different inquiries and we find different things——

Senator MERKLEY. I know you are not a decider on that type of issue, but I am sure you are familiar with the general law. Is that allowed under the law for one company to pay another to keep a device off the market?

Dr. WOODCOCK. I do not know actually.

Senator MERKLEY. You do not know?

Dr. WOODCOCK. I am not a lawyer. I am a doctor.

Senator MERKLEY. It certainly is the type of issue that has been widely discussed in the public sector of companies paying other companies to keep their products off the market.

Dr. WOODCOCK. Okay.

Senator MERKLEY. And also buying up other companies to keep their products off the market.

So in your interest in seeing—you mentioned—and I do not want to put words in your mouth, but that essentially you referred to generics having a potentially powerful, positive effect on lowering the cost of drugs.

Dr. WOODCOCK. Right.

Senator MERKLEY. So in the interest, should Congress be looking at making sure that there are not strategies in which name brand drug companies keep generics off the market?

Dr. WOODCOCK. Yes. We believe that we are subject to some of these, as Senator Collins was talking about with the problems getting the reference listed drug, the brand drug, to do the bioequivalence studies, sometimes using the REMS, our restricted program for safety, as a reason not to give the product out.

Senator MERKLEY. Indeed, I was appalled to hear that, that somehow a name brand company can prevent their competitor from getting enough of the drug to do the very studies that you are requiring. And should that not be grounds for them being penalized in some way for essentially—that is another strategy to prevent a competitor legally entering the marketplace.

Dr. WOODCOCK. Yes. Well, we have certainly been talking to members of Congress about these problems. We have a long history of citizen petitions, which Congress had taken some actions on before, filing of citizen petitions to prevent the availability of generics based on various scientific issues that are raised.

Senator MERKLEY. Is Auvi-Q currently trying to get approval for a modified product to address the dosing issues that it had?

AUVI-Q

Dr. WOODCOCK. I am not allowed to discuss anything like that.

Senator MERKLEY. So if they were attempting to do so, would you be prioritizing their application?

Dr. WOODCOCK. If we were doing that, if another new drug application came in, because that is not a generic, those have a very rapid time frame already for review and approval.

Senator MERKLEY. So we are talking about a combination product. The drug is already approved. So it is really just the device. You are saying it would be fast-tracked if they were to reapply with a modified device to address the dosage issue that they had previously.

Dr. WOODCOCK. I am saying that it would be under the new drug review process, which is governed by the prescription drug user fee timelines, which is very speedy.

PRIORITIZATION OF DRUG APPLICATIONS

Senator MERKLEY. You have authority in cases where there is market dysfunction to prioritize applications. Is that correct?

Dr. WOODCOCK. Market dysfunction I do not think enters into our statutory language. What we have done under our procedures for generics is we prioritize for public health——

Senator MERKLEY. Let me put it differently. When there is a single product in a marketplace and the costs are so high people cannot afford it, do you have the ability to help address that by prioritizing an application whether it is a competitor or a generic—a competitor name brand or a generic, put that at the top of the list to try to address a big problem faced by millions of Americans who cannot afford the drug and whose lives are at risk as a consequence? Do you have the ability to prioritize that?

Dr. WOODCOCK. We do prioritize that for generics where there is a single source, whether it is——

Senator MERKLEY. How about for a competitor?

Dr. WOODCOCK. We do not have a procedure to do that.

EPINEPHRINE AUTO-INJECTOR MARKETPLACE RE-ENTRY

Senator MERKLEY. So we have heard some real horror stories about devices getting approved. So if a company comes back and they say, hey, we had a slight manufacturing defect that caused us to have a dosage problem, we have fixed it, here is our new version, are you going to send them out for clinical trials that cost $10 billion—I am exaggerating—and 10 years, or are they going to be able to get that modification approved and back on the market?

Dr. WOODCOCK. If you are talking about an epinephrine auto-injector, they really do not need clinical trials. This is not—you need to show that you are injecting the epinephrine where it is supposed to go and that you can do that reliably every time under emergency circumstances.

Senator MERKLEY. Right. I am trying to get some sense of how much money, how much time for a slight modification of an injector, because their injector had a problem. Is that a big obstacle for them reentering the market?

Dr. WOODCOCK. I do not know about a big obstacle. They may have to do——

Senator MERKLEY. How much time? How much money in general terms? The public would like to understand how big the obstacle is posed by the FDA to enable the market to function. I understand it is very important that things work. It is also very important that there be a functioning system to allow products to get back on the market. How much time? How much money would it take?

Dr. WOODCOCK. I would say the time might it take them, if they were able to solve—this theoretical company—a manufacturing problem, and they had to change things, depending on how they change their auto-injector, then they might have to do a human factor study again to make sure that people could use it properly. Or they might not. If the change was just inside, they might not have to do that. But if the change was how you actually went about injecting yourself, they might have to test that again on people to make sure that it would work for them.

Senator MERKLEY. I am just hoping there is some common sense. We are talking essentially about a pre-loaded syringe that costs $600 and people cannot afford it. It should not be impossible to enter the market. I encourage you—I am just wrapping up, so I will turn this back to you—to ponder from that direction of whether there are unreasonably difficult, expensive procedures that make it very hard for competitors to enter the market because clearly, if it was easier, there would be people entering the market and we would not have this problem.

And then we have all these tricks of the system in which the name brand is seeking to prevent those competitors. And if you essentially have procedures that are complicit in that, that is a problem. We really need to examine that very, very carefully because it is not this one drug. This is a whole systemic problem in our drug approval process, and the price of drugs are making health care the most expensive in the world here in the United States, out of reach to millions of Americans. They bypass their drugs because they cannot afford to buy them under their deductible. It is a very big deal.

Thank you.

GENERIC DRUG APPROVAL WORKLOAD

Senator MORAN. Doctor, I think we are about to wrap up our hearing, assuming I do not talk so long that other members and other Senators arrive.

Just a couple of follow-ups. I indicated in my opening statement that at least the understanding is that the FDA is close to finalizing negotiations with the industry on a new round of fees and regulatory requirements. You indicated in your response to my question that—again, it goes back to the definition of a backlog. This is a process by which it takes a number of steps.

Dr. WOODCOCK. That is right.

Senator MORAN. Are you able to tell me? Is that part of the negotiations with the industry? From their perspective, I do not know one way or another whether they would say the same thing that you indicated. Were there issues that could be negotiated with the companies in this process that reduce the number of times it is necessary to have the application reconsidered?

Dr. WOODCOCK. Well, I think that is definitely on their mind and our minds. To Senator Merkley's questions, one of the things that we need to do is get a process for generics where we give advice to complicated generics before they come in and send in an application. That is what we negotiated under the Prescription Drug User Fee Act for the new drugs, and that is something that there is great interest in, in having a program so that for these complicated things—it is not just a pill—we can interact with companies and give them advice and tell them what to do.

So both this workload—let us not call it a backlog, but our large workload we have now, part of which is inherited from the things that are cycling multiple times, is on everyone's mind, and it is definitely part of our discussions, how to deal with that.

Senator MORAN. Can you report anything about the status of those negotiations, or is that beyond your——

Dr. WOODCOCK. I could say with the industry, they have concluded. Obviously, there are many other steps. We would have to have a public meeting as described in the statute, and then, of course, we will hope to provide the consequences to Congress.

Senator MORAN. Is there a timeframe in which you would expect that consequences to Congress to occur?

Dr. WOODCOCK. I think that was written in the statute. If you will excuse me, I will ask my colleague here.

Sorry. I wanted to give you accurate information.

We hope to post those notices soon, and then we would transmit to Congress by January.

Senator MORAN. And that is your expectation?

Dr. WOODCOCK. I would certainly hope so, yes.

DUCHENNE MUSCULAR DYSTROPHY

Senator MORAN. I also mentioned that you were able—I know this is not a generic drug, but we were talking about Duchenne and the muscular dystrophy drug. It is not a generic, but at least the reports are that you found a way to accelerate the process. Is that an accurate analysis or statement or description of what occurred?

Dr. WOODCOCK. The description of what occurred is that the product was approved under something called accelerated approval. That may be a little bit of a misnomer, but that is what it is called. What it means is you do not have clinical trials that showed the produce gave benefit to patients. You approve it on a surrogate endpoint that we feel is reasonably likely to predict clinical benefit. That is how we approved a lot of HIV drugs over the years, and cancer drugs and many other drugs have been approved under accelerated approval. Then the company has to prove with later studies that the product really does have the predicted benefit.

Senator MORAN. Is there anything to learn from that process that would apply to generics?

Dr. WOODCOCK. I do not think so because that has to do with showing effectiveness, and generics get their effectiveness by showing they are the same as the reference drug.

Senator MORAN. So a different standard.

Dr. WOODCOCK. Yes.

Senator MORAN. And the generic ought to be more easily met?

Dr. WOODCOCK. Yes. The generic does not have to do clinical studies. In fact, they are not allowed to do clinical studies of efficacy or else they cannot be a generic.

Senator MORAN. Doctor, do you have anything you would like to tell us that we have not gotten from you from our questioning?

Dr. WOODCOCK. Well, I do think that we are very focused on making sure that any drugs that can be approved and are safe and effective can get on the market, that the pathways are clear, that there are not unnecessary barriers to getting on the market. However, I would say that our standards have to do with making sure those drugs work for patients and that they are reasonably safe and that they are of adequate quality so that the drug supply in the United States is a very reliable, high quality drug supply. And we do try to expedite where we can to improve availability. We are sensitive to that.

ADDITIONAL COMMITTEE QUESTIONS

Senator MORAN. Dr. Woodcock, thank you very much for your testimony today. In my view, this hearing was what a congressional hearing in most instances should be, an opportunity to be educated and to learn. And you have certainly helped me in that process.

For members of the subcommittee, any questions that you would like to submit for the hearing record should be turned into the subcommittee staff within 1 week, which is Wednesday, September the 28th.

And we would appreciate it, Doctor, if FDA could respond within 4 weeks thereafter.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

SAFETY PROTOCOLS FOR PRODUCTS WITH RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

Question. Who has the most appropriate expertise to determine the safety protocols necessary for safe bioequivalencey testing? For example, if a product has a REMS with elements to assure safe use, and the FDA has made a determination that those elements are necessary to ensure the benefits of the drug outweigh the risks (taking into account that the absence of those elements to assure safe use the agency would be unable to approve the product). Do these determinations fall under the control of the FDA, or can/should these issues be decided through the judicial process—ie with courts and juries?

Answer. FDA determines what safety measures are necessary for approval of a drug product, including whether a risk evaluation and mitigation strategy (REMS) should be required for any particular product. A REMS will only be imposed if FDA—based on its assessment of the relative risks and benefits of the drug—determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. If FDA makes a determination that a REMS is necessary for approval of a particular product, FDA also determines each of the specific elements that the REMS must contain in order to address the safety issues associated with the product.

Given that FDA determines whether a REMS is necessary and what specific safety protections the REMS must contain, FDA has the most appropriate expertise to determine whether the protocols submitted by a generic company for bioequivalence testing contain safety protections comparable to those in the REMS.

COST OF DOING BUSINESS

Question. During questioning by Senator Collins about restricted distribution systems preventing access to samples by generic drug manufacturers, Dr. Woodcock indicated that a solution to this problem which included providing FDA with the authority to penalize brand drug manufacturers for denying access to samples with fines might not be effective, as brand drug companies might not alter their behavior and view the fines as "a cost of doing business." It is my understanding that the FDA has the authority to penalize conduct beyond mere fines, including the levying of civil monetary penalties (CMPs).

Are you aware of instances where brand drug manufacturers decided to pay civil monetary penalties to FDA and not correct their behavior and come into compliance with the FFDCA? In other words, are you aware of any instances where brand drug manufacturers decided purposefully to violate the act after the imposition of CMPs, and consider the CMPs as "a cost of doing business?"

Answer. To date, FDA has not assessed penalties for brand drug manufacturers under the FFDCA, so we do not have specific examples of the type requested.

RISKS OF COUNTERFEIT AND UNAUTHORIZED DRUGS COMING IN FROM OVERSEAS

Question. I understand that the FDA's Office of Criminal Investigations includes in its mission protecting American citizens from the risks of counterfeit and unau-

thorized drugs coming in from overseas. For example, in one case the FDA helped prosecute in 2013, the defendant smuggled more than $12.4 million in non-FDA approved chemotherapy drugs and injectable cosmetic drugs and devices. Many of these drugs were subject to strict temperature controls to protect drug potency, but the defendant shipped them without the dry ice used by legitimate distributors and one shipment took more than two weeks to arrive in Virginia from overseas during a heat wave in 2012. While not all of the investigations result in criminal convictions such as this one, they do all help impede this dangerous, illicit flow of drugs. Dr. Woodcock, I would appreciate your assurance that the FDA will continue to make it a priority to protect Americans in this manner. I would also appreciate periodic updates from the FDA on its enforcement activities in this area.

Answer. FDA is committed to protecting U.S. consumers against unsafe and ineffective drugs, including those that come in from overseas. We recognize that the importation of unapproved drug products, some of which might be counterfeit or substandard, poses a risk to Americans' health. We are also aware that adverse events flowing from the importation of such unapproved products could lead to diminished confidence in FDA-approved products. The Agency is taking steps to bolster the security of the drug distribution system through its implementation of Title VII of the Food and Drug Administration Safety and Innovation Act and the Drug Supply Chain Security Act. Information about our implementation of these statutes is available on the Agency's Web site at http://www.fda.gov/AboutFDA/Transparency/track/ucm328907.htm and http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm388726.htm, respectively. For information about our enforcement activities involving unapproved drug products from overseas, please visit the Web page for FDA's Office of Criminal Investigations: http://www.fda.gov/ICECI/CriminalInvestigations/default.htm.

QUESTIONS SUBMITTED BY SENATOR JON TESTER

Question. What challenges does the FDA face when trying to improve the efficiency of the generic drug application review process?

Answer. By far the biggest challenge FDA faces when trying to improve the efficiency of the generic drug application review process is multiple review cycles. Historically, it takes on average 3.8 review cycles to approve an abbreviated new drug application (ANDA). A review cycle begins each time an applicant submits an ANDA for FDA review. If the ANDA does not meet FDA's standards, then FDA will not approve it, but instead will communicate deficiencies to the applicant. The applicant then addresses the deficiencies and re-submits the ANDA in the form of an ANDA amendment to FDA. The back and forth continues until the ANDA is approved (or withdrawn).

One reason for this, is known as the "file first, fix later" approach. The applicant does not know what FDA is looking for, submits an incomplete application, and relies on FDA as a consultant, iteratively, to improve the submission until it becomes approvable. The proposed GDUFA II agreement targets this problem. Among other things, the agreement would enhance the pre-ANDA program for complex products to clarify regulatory expectations earlier in product development and help applicants develop more ANDAs that are "right the first time."

The other main reason for multiple review cycles is that the ANDA review process until recently was under-developed. FDA and Industry spent a great deal of time working together to improve it over the past several years. The proposed GDUFA II agreement is much more prescriptive about how each stage of the ANDA review process would work, from start to finish. Roles and responsibilities, sequencing, and timelines are clearly delineated. Enhanced communications would give applicants many more opportunities to address deficiencies within a review cycle, instead of deferring the work until a later review cycle.

Question. Would increased funding help the FDA review generic drug applications more quickly, or does it need additional authorities from Congress? If lack of funding is an issue, to which specific programs or initiatives should the Appropriations Committee consider directing increased resources? If lack of authority is an issue, what legislative fixes should Congress consider?

With respect to funding, FDA and industry recently negotiated a proposed GDUFA II agreement, pursuant to which industry would pay FDA approximately $493.8 million per year, adjusted for inflation, each year for the next 5 years. In exchange, FDA commits to achieve agreed-upon metric goals for the review of generic drug submissions and make numerous other significant program enhancements.

Additional funding directed to the generic drugs program would enhance FDA's capacity to support the review of generic drug submissions.

With respect to new or modified authorities, FDA is currently evaluating the extent and nature of industry conduct intended to frustrate and delay generic competition.

Question. What impact has the backlog of generic drug applications had on the prices of prescription drugs? How much of the rising costs of drugs is attributable to the backlog?

Answer. First and most importantly, the generic drug program decreases, not increases, drug costs. According to the IMS Institute for Healthcare Informatics, generics saved the U.S. healthcare system $1,680,000,000,000 from 2005–2014. The generic drug program has been an extraordinary success at expanding access to affordable medicines.

FDA does not agree that there is currently a backlog of generic drug submissions pending at FDA. There was a backlog of generic drug applications in fiscal year 12, prior to the start of the GDUFA program. At the beginning of fiscal year 12, about 2,800 submissions were pending at FDA and about 100 were pending with Industry. Pursuant to GDUFA, the Agency committed to take action on 90 percent of these pre-GDUFA backlog submissions by the end of fiscal year 17. FDA achieved that goal 15 months ahead of schedule.

At present, there are about 2,200 applications pending at FDA. Virtually all applications submitted before fiscal year 16 are under active review, meaning FDA has communicated at least one deficiency to the applicant. FDA is currently achieving record levels of output, and these increases are expected to continue. While there are more applications than FDA would like to have in process, it is important to note, the generic pipeline needs to contain a certain volume of submissions. Zero submissions would indicate that no one is developing new generic products.

There are also currently about 1,700 applications pending with Industry. FDA can't act on these submissions until applicants correct deficiencies and re-submit them to us. Forty percent of these applications have been pending with Industry for more than 8 months, and 27 percent of them have been pending with Industry for more than a year.

Considering pending abreviated new drug applications (ANDA) is only part of the big picture.

—65 percent of innovator drugs have some form of FDA-approved competition.

—For 24 percent of innovator drugs, FDA has not yet approved a generic, because by law the innovator is still protected by patents or exclusivity.

—For 10 percent of innovator drugs, FDA has not approved a generic because FDA has not received a generic application. These are generally small markets with low reimbursement where companies do not perceive an opportunity to make money.

—For 2 percent of innovator drugs, there is a pending, unapproved ANDA.

Even after FDA approves a submission, a company may not market it. Generic companies frequently defer marketing pursuant to patent settlement (so-called "pay to delay") agreements. In addition, while marketing typically reduces price, it does not always.

Question. For what commonly-used prescription drugs do patients not have access to an effective and interchangeable generic alternative? What steps can the FDA take to address this lack of generic alternatives?

Answer. There are many commonly-used prescription drugs where FDA can lawfully approve a generic (because patent/exclusivity bars to approval have expired), and FDA has received an ANDA that is not yet approved.

To increase the number of ANDA approvals, FDA proposes to reauthorize the generic drug user fee program. FDA also has funded regulatory science projects to help develop the science needed for generic drug development. In addition, the Agency is currently evaluating industry practices that delay access to generics.

In many cases when there is no approved generic product, it is either because patent and exclusivity have not expired for the innovator product and FDA can't lawfully approve a generic or because FDA has not received a generic drug application in the first place. That is, the obstacles are often legal and economic, not regulatory or scientific. As for FDA, the Agency determines whether it can approve a generic but companies decide whether to market them or to defer marketing, sometimes pursuant to a settlement agreement with the brand drug company.

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

Question. One reason consumers face high drug prices is that some brand name pharmaceutical companies have used inappropriate delay tactics to limit the ability of generic competitors to enter the market. For example, some brands refuse to provide samples needed for testing by generic manufacturers. You discussed this issue briefly during the hearing and expressed concern about the incentives brands may have to use tactics such as these to delay market entry.

Can you explain what role access to these samples plays with respect to market competition and lower cost drugs?

Answer. Generic competition can significantly lower the price of a drug product. To obtain approval for a generic drug, however, the generic company must show, among other things, that its version of the drug product is bioequivalent to the brand drug (also called the "reference listed drug," or "RLD"). This usually requires the generic company to do bioequivalence studies comparing their product to the RLD. To do these studies and submit a generic application, they need to get access to samples of the RLD.

Typically, generic companies are able to get samples of the RLD through normal distribution channels (i.e., via wholesalers). But sometimes they cannot because limitations on the distribution of the drug are in place. RLDs may be unavailable through normal distribution channels because the brand company limits the distribution of the product on its own initiative. In other cases, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) (such as a pharmacy certification requirement) might impact the way the product is distributed.

Question. What is the magnitude of this problem?

Answer. FDA has received more than a hundred inquiries from generic companies that want to develop generic drugs but tell us they are unable to do so because they cannot get supplies of the RLD to do testing. Many of these brand drug products are quite expensive. A significant majority are listed online at a retail price of over $600 per patient per month, and many are in the range of thousands of dollars per patient per month. These inquiries have involved both REMS and non-REMS products.

Question. What is the most effective way to assure that generic companies can obtain the samples necessary for bioequivalence testing? Is a legislative solution required?

Answer. Legislation that creates a clearly defined pathway and legal obligation for RLD access, coupled with a strong remedy to deter brand companies from blocking access to samples of the RLD could help significantly to facilitate and expedite generic development.

Question. What role should the FDA play in the process of obtaining samples by generic companies?

Answer. FDA has issued draft guidance describing the Agency's current views on its role in facilitating the provision of RLD samples for bioequivalence testing (see draft guidance for industry on How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD (Protocols Guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425662.pdf).

As described in the Protocols Guidance, in cases where limitations on the distribution of a drug product occur in connection with a REMS, FDA (upon request) reviews the bioequivalence study protocols, informed consent documents, and informational materials submitted by the generic company to ensure that they have safety protections comparable to those in the applicable brand REMS. Once we've determined that they do, we send the brand company a letter ensuring them that selling the RLD to the generic company for testing and development will not be considered a violation of the REMS.

We also encourage companies to contact the Federal Trade Commission if they believe a company's refusal to sell samples to them constitutes anticompetitive behavior. This is a recommendation that we also make to companies that inquire about products for which the distribution limitations are voluntarily imposed by the brand company with no REMS in place (for which we do not conduct a protocol review).

Question. Some have suggested that providing access to samples of prescription drugs with known safety risks to generic companies for bioequivalence testing endangers patients. Are these concerns well founded? Are additional protections, such as increased regulatory requirements, necessary to ensure patient safety?

Answer. FDA does not believe that the concerns about bioequivalence testing are well-founded, nor does FDA believe that protections beyond those described in the Protocols Guidance are necessary to ensure patient safety. FDA notes that bio-

equivalence testing typically involves a relatively small number of human subjects and a small number of doses (often only one dose) and, therefore, a lower level of risk. The regulatory regime applicable to bioequivalence testing—including the exemption of most bioequivalence testing from the IND requirements—reflects the generally lower level of risk associated with bioequivalence testing when compared with other kinds of clinical testing that occur during the drug development process. Additionally, the protections in the REMS are designed to mitigate risks that occur during real world, every day use by patients, and safety concerns are likely to be lower in the more tightly-controlled context and limited scope of bioequivalence testing.

Further, FDA regulations (at 21 CFR Part 56) require that before bioequivalence testing can begin, it must be reviewed and approved by an Institutional Review Board (IRB) to ensure that risks are minimized. The steps outlined in FDA's Protocols Guidance provide additional confirmation that the bioequivalence study protocols contain safety protections comparable to those in the REMS for the brand product. We do not believe that additional steps are necessary at this time.

Question. Recent headlines have highlighted pharmaceutical company Mylan's dramatic price increase of the EpiPen auto-injector. With a more than 480 percent price increase on a two-pack of EpiPens since 2009, consumers—including parents, first responders, and school leaders—have faced financial difficulty in obtaining this lifesaving and necessary drug. There are currently no approved generics on the market in the United States, but Mylan claims it will soon launch a generic EpiPen at a reduced price.

Can you provide the Committee with an estimate for how many generic alternatives to the EpiPen are being reviewed by the agency and at what stage of review each product currently stands?

Answer. To date, FDA has approved four epinephrine auto-injectors: EpiPen, Twinject, Adrenaclick, and Auvi-Q. Twinject is no longer marketed. Auvi-Q was voluntarily recalled by the manufacturer in October 2015. EpiPen is being marketed and has the large majority of market share at this time. The application holder for Adrenaclick has chosen to market Adrenaclick without a trade name, i.e., as an 'authorized generic' to Adrenaclick. There are currently no approved generics for epinephrine auto-injectors.

FDA is restricted from disclosing to the public confidential information about applications pending before the Agency. Although FDA may not disclose this information, a sponsor is able to disclose information about its products, and can share any communication received from FDA concerning any of its products. Teva and Sandoz have publicly acknowledged that they have submitted abbreviated new drug applications (ANDAs) listing EpiPen (epinephrine injection) as the reference listed drug (RLD). However, consistent with longstanding Agency practice, we do not discuss the substance of matters pending before the Agency. Such a practice helps to ensure the integrity of the review process.

As a general matter, we note that FDA's Office of Generic Drugs has a prioritization and expedited review policy for certain generic drug applications, including potential first generics. This policy is set forth in the Center for Drug Evaluation and Research's Manual of Policy and Procedures (MAPP) 5240.3, Revision 2, "Prioritization of the Review of Original ANDAs, Amendments and Supplements."[1] Pursuant to our prioritization policy, ANDAs for drugs from generic applicants that have "first filer" status or that are otherwise eligible to be the first generic approved are often prioritized and given expedited review.

Question. EpiPen is a drug/device combination product that incorporates a drug that is no longer under patent into a device for which Mylan still has patent protection. What is the process the agency uses to approve generic applications for drug/device combination products? What criteria are considered to determine equivalence? Are there any generic drug/device combination products on the market, including but not limited to epinephrine auto-injectors?

Answer. In determining whether to approve an ANDA referencing a drug-device combination product such as EpiPen, FDA considers the same factors as are required for all ANDAs.[2] More specifically, a generic drug applicant seeking approval of a drug-device combination product, such as an epinephrine auto-injector, will need to demonstrate that its proposed generic product is bioequivalent to the RLD.

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[1] For more information, please see http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.

[2] EpiPen is categorized as a drug-device combination product, with a drug primary mode of action. As a result, the Center for Drug Evaluation and Research (CDER) would be the lead FDA center from a review and jurisdiction perspective, while the Center for Devices and Radiological Health (CDRH) would be consulted for review of the device component of the product.

In addition, a proposed generic product must generally contain the same active ingredient, same route of administration, same dosage form, same strength, and (with certain permissible differences) same labeling as the RLD. An ANDA is generally not required to be the same as the RLD in certain other respects (e.g., it can differ in inactive ingredients or container closure system). However, where differences in these aspects of the products are significant enough that they require clinical studies to demonstrate safety or effectiveness of the proposed generic drug, or necessitate such significant labeling differences that the generic drug labeling is no longer "the same" as the RLD's, FDA will deny approval of the proposed generic product.

FDA's assessment of a device constituent part of a proposed generic product is made on an application-by-application and product-by-product basis in the context of the review of a specific generic drug application. FDA will evaluate the significance of any design differences between the innovator product (RLD) and a proposed generic product in light, among other things, of the intended users and uses of the product, including the environment in which such product is used and in light of the requirements for an ANDA to have, among other things, the same labeling as the RLD.

As noted above, there are currently no approved generics for epinephrine auto-injectors. Although Mylan has announced publicly its intention to market an "authorized generic" of EpiPen,[3] it is important to clarify that these statements have not indicated that Mylan is intending to market a generic version of EpiPen under an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires the submission of an abbreviated new drugapplication and FDA's approval of such application prior to the marketing of such generic product. Rather, Mylan intends to market an "authorized generic" of EpiPen. An authorized generic is made under the brand name's existing new drug application using the formulation, process, and manufacturing facilities approved for use by the brand name manufacturer. The labeling of the brand name product is changed to remove the brand name or other trade dress. An authorized generic is not synonymous with an FDA-approved generic, the latter of which requires a separate application and approval from that of the brand name product.

FDA has approved ANDAs for several different drug-device combination products. These include ANDAs for sumatriptan injection (RLD: Imitrex STATdose Injection), mometasone furoate nasal spray (RLD: Nasonex Nasal Spray), sumatriptan nasal spray (RLD: Imitrex Nasal Spray), triamcinolone acetonide nasal spray (RLD: Nasacort AZ Nasal Spray), fluticasone nasal spray (RLD: Flonase Allergy Relief Nasal Spray), and norelgestromin and ethinyl estradiol transdermal system (RLD: Ortho Evra Transdermal System).

Question. In addition to expanding the availability of generic alternatives on the market in order to reduce out-of-pocket costs for consumers, it is critical that generic manufacturers take the necessary steps to ensure the safety of their products. In 2013, Congress urged the FDA to revise its rules to require generic drug manufacturers to promptly update their labeling to include new safety information. In response to the Supreme Court ruling in PLIVA v. Mensing, which held that generic drug companies could not be sued under state law over a failure to provide adequate labeling about potential drug side effects, consumers have had no remedy in the event they are injured as a result of outdated generic labeling.

In November 2013, the FDA released a proposed rule which recognized the importance of generic manufacturers being held accountable for outdated and incorrect labeling. Unfortunately, the agency has yet to finalize this critically important Proposed Rule.

Can you provide the Committee with an update on the agency's finalization of its Proposed Rule on generic labeling?

Answer. The proposed rule is intended to improve the communication of important drug safety information to healthcare professionals and patients. FDA has received a great deal of public input from stakeholders during the comment period on the proposed rule regarding the best way to accomplish this important public health objective.

FDA is carefully considering comments submitted to the public docket established for the proposed rule from a diverse group of stakeholders including: consumers and consumer groups, academia (including economists), healthcare associations, drug and pharmacy associations, brand and generic drug companies, law firms, state governments, and Congress, including comments proposing alternative approaches to

[3] See Mylan Press Release (Aug. 29, 2016), http://newsroom.mylan.com/2016–08–29–Mylan-to-Launch-First-Generic-to-EpiPen-Auto-Injector-at-a-List-Price-of-300-per-Two-Pack-Carton-a-More-than-50–Discount-to-the-Brand-Product.

communicating newly acquired safety-related information in a multi-source environment (see Docket No. FDA–2013–N–0500). These comments include a summary of FDA's meeting with the Generic Pharmaceutical Association (GPhA) on September 8, 2014, to listen to their comments and views regarding the proposed rule. In addition, FDA held a public meeting at which any stakeholder had the opportunity to present or comment on the proposed rule, or on any alternative proposals intended to improve communication of important, newly acquired drug safety information to healthcare professionals and the public. In the February 18, 2015 notice announcing the public meeting, FDA reopened the docket for the proposed rule until April 27, 2015, to allow the submissions of written comments concerning proposals advanced during the public meeting. FDA will determine next steps based on our analysis of comments on the proposed rule and additional information submitted as part of the public meeting.

CONCLUSION OF HEARING

Senator MORAN. Again, I thank everyone for their attendance today, and I will conclude this hearing. The meeting is adjourned.

[Whereupon, at 4:12 p.m., Wednesday, September 21, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]