

DRUG SAFETY: AN UPDATE FROM THE FOOD AND DRUG ADMINISTRATION

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED ELEVENTH CONGRESS SECOND SESSION

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DRUG SAFETY: AN UPDATE FROM THE FOOD AND DRUG ADMINISTRATION

WEDNESDAY, MARCH 10, 2010

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

The Subcommittee met, pursuant to call, at 2:17 p.m., in room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (Chairman of the Subcommittee) presiding.

Members present: Representatives Pallone, Dingell, Eshoo, Green, DeGette, Matheson, Barrow, Christensen, Sarbanes, Murphy of Connecticut, Braley, Waxman (ex officio), Whitfield, Shimkus, Buyer, Pitts, Myrick, Murphy of Pennsylvania, Burgess, Blackburn, Gingrey and Barton (ex officio).

Staff present: Phil Barnett, Staff Director; Bruce Wolpe, Senior Advisor; Ruth Katz, Chief Public Health Counsel; Sarah Despres, Counsel; Rachel Sher, Counsel; Elana Stair, Policy Advisor; Katie Campbell, Professional Staff Member; Stephen Cha, Professional Staff Member; Virgil Miller, Professional Staff Member; Allison Corr, Special Assistant; Eric Flamm, FDA Detailee; Greg Dotson, Chief Counsel, Energy and Environment; Dave Leviss, Chief Oversight Counsel; Karen Lightfoot, Communications Director, Senior Policy Advisor; Lindsay Vidal, Special Assistant; Mitchell Smiley, Special Assistant; Clay Alspach, Minority Counsel, Health; and Ryan Long, Chief Counsel, Health.

Mr. PALLONE. The meeting of the subcommittee is called to order, and today we are having a hearing on "Drug Safety: An Update from the FDA."

I think before I give my opening statement, I am going to recognize my colleague, the ranking member of the full committee, the gentleman from Texas, Mr. Barton.

Mr. BARTON. Thank you, Chairman Pallone. I just need to make an announcement to the subcommittee. The ranking Republican on the subcommittee is Congressman Nathan Deal of Georgia. As we all know, he announced several weeks ago his intention to resign effective last week. He has since withdrawn the effective date of his resignation until after the vote or votes on the House Floor concerning the comprehensive health care bill. But during that time, Congressman Deal is not planning on attending Congress or at least the subcommittee of which he is the ranking member. Therefore, today I am nominating Congressman Shimkus of Illinois to be the temporary ranking member. That is unofficial obviously because there is no such thing as temporary anything, but he will as-

sume the duties of Congressman Deal until such time as Mr. Deal does effectively resign. When that happens, I will inform Mr. Waxman that it is my intention to make Mr. Shimkus the ranking member of the subcommittee subject to committee approval of such designation. So for today's hearing and any subsequent hearings that this subcommittee has, until Mr. Deal actually resigns, Mr. Shimkus will assume the duties of the ranking member of this subcommittee.

Mr. PALLONE. Well, thank you, and let me congratulate Mr. Shimkus. He has always been very helpful and tried to work in many cases on a bipartisan basis, so I am very happy to welcome him as the new or acting ranking member. I was going to ask, though, the way you described that, Mr. Barton, it sounded like Mr. Deal might still be here for a while, depending on the circumstances.

Mr. BARTON. It is up to you.

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

Mr. PALLONE. All right. We will have to see. I shouldn't say that actually. He probably won't be here for very long based on what I believe, but we will see. In any case, congratulations.

Let me recognize myself for an opening statement. As I mentioned, today the subcommittee is meeting to discuss drug safety. It has been at least a year since our last hearing on this issue and we are here to get an update and overview from the FDA on current challenges and successes with respect to drug safety. Recently there have been a number of drug-related incidents that have shaken public confidence in the FDA's ability to ensure that consumers are using safe and effective drugs. In addition, reports from the Institute of Medicine and the Government Accountability Office highlight the shortcomings of our current system and provide guidance on how to strengthen the drug safety laws to better protect the American public.

In response to the incidents, Congress passed the FDA Amendment Acts of 2007, or FDAAA, I guess it is pronounced. This bill was aimed to provide the FDA with additional authorities, specifically post-approval authorities that would help the agency keep drugs safe for consumers to use. For example, the bill provided the FDA with the authority to require drug manufacturers to conduct post-approval studies that would monitor drugs for safety as they are used in the broader population. The bill directed the FDA to establish a post-market surveillance system to improve the agency's ability to detect and act upon drug safety problems and gave the FDA the authority to require drug label changes for safety reasons. It also provided the FDA with the authority to impose Risk Evaluation Mitigation Strategies, or REMS, for drugs and biologics when necessary, and these REMS are designed to manage known or potential serious risks with a drug or biologic to ensure that the benefits of the product outweigh the risks it poses to the patient.

Now, the FDA is here today to talk about how effective this law is in protecting the American people from unsafe drugs, and I am particularly curious to hear about the progress on the implementa-

tion of some of the post-approval authorities and to learn from the agency of potential stumbling blocks or challenges that will require further Congressional action.

Outside of the FDAAA realm, however, we already know that we need to do more to ensure the safety of our drugs. We all remember that horrible incident in early 2008 that again intensified this committee's focus on drug safety. Baxter Health Care Corporation, one of the manufacturers of the blood thinner heparin, which is used to prevent blood clots, began noticing an increase in the number of adverse effects associated with their product. After further investigation, it was determined that the Baxter heparin contained a counterfeit ingredient that mimics an ingredient normally used in heparin production but that is highly toxic and dangerous to humans. Baxter had received this ingredient from a manufacturer in China, and upon further investigation by the FDA, it was determined that due to a processing error at the agency, this Chinese manufacturer had never been inspected by the agency. Tragically, 81 individuals lost their lives as a result of the contamination. Obviously this should not and cannot happen again and we must do everything we can to ensure that it does not happen again. And I am curious to hear the FDA's thoughts and plans for improving import and supply chain safety, especially since the GAO found that roughly 80 percent of the active ingredients used in drugs are actually manufactured abroad.

I and a few of my colleagues on the Energy and Commerce Committee introduced a bill this Congress that aims to provide the FDA with additional funding authorities to better regulate the imported materials used in drugs. The bill would also place more responsibility on the manufacturers to ensure that the ingredients they are using are safe. As highlighted by the heparin case, we know the devastation that can come from an unsafe drug supply chain.

So I am looking forward to hearing from today's witnesses.

I now recognize our new ranking member, my friend, Mr. Shimkus.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Chairman Pallone. Thank you for your warm welcome. I want to thank Ranking Member Barton for his trust and confidence in me, and I look forward to continuing to work hard on behalf of the committee and really the work we need to do here.

The FDA, with all the challenges and the inspection that we do, it is still really the gold standard for health and safety in the world. A lot of countries don't have to do all the research and the testing because we in essence do it for them, so although we will be inquisitive and we will be trying to ask questions, I put that first on the table because they world does rely on what we do here. And we have spent a great deal of time on the issue of drug safety and the Food and Drug Administration Amendments Act, and I look forward to Dr. Sharfstein. Welcome, and I look forward to your updates. And I want to continue to learn more about the Risk Evaluation Mitigation Strategies, known as REMS, how that is pro-

gressing and whether information is being disseminated in a user-friendly manner. I am all about risk-based approach. The bills that we passed in a bipartisan, I continuously spoke out on risk-based programs. So I am very interested in that.

Your projections for advisory committee members in the future and those projections, I believe it is important to maintain credibility and expert participants. Recent stories indicate the exception reductions provisions may be diluting the advisory committee's ability to serve in those functions, and we do want highly qualified and the best people to be helpful.

But in general we know gaps remain when it comes to ensuring the safety of drugs in the United States and I remain committed to addressing those needs along with Chairman Pallone. One thing I know about my colleagues on the other side, they are tenacious in moving in that direction and we want to be helpful in that manner. The FDA continues to make progress in utilizing risk-based systems like PREDICT and I am curious how this might translate in regard to targeting facility inspections. Regardless of the end result, we know that the FDA needs proper funding. We need to identify where we can cut out wasteful spending and make sure funding to ensure the safety of food and drugs in this country does not take a backseat with our appropriators.

Lastly, echoing remarks I made in the past, I hope we can work towards these goals using a prudent formula to get a good bipartisan product. Chairman Waxman, Chairman Emeritus Dingell, Chairman Pallone and Chairman Stupak working along with Ranking Member Barton, Deal and myself came up with the food safety bill that ultimately passed the House really in a huge bipartisan manner, and I think we can do that if we move forward in that direction.

I look forward to continuing our work to get legislation signed into law and hope we can use the successes of food safety as our motto in any drug safety-related legislation.

Thank you, Mr. Chairman. I yield back my time.

Mr. PALLONE. Thank you, Mr. Shimkus.

Next is our full committee chair, Chairman Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Chairman Pallone, for holding this hearing today and giving us the opportunity to hear from the FDA on the critically important issue of drug safety.

It has been some time since we focused on drug safety, but we did indicate that we wanted to take up this bill after food safety, which was the first step, and now we are going to turn to drugs, medical devices and cosmetic safety issues.

We can't forget the lessons of the 2007 heparin contamination catastrophe which resulted in numerous severe allergic reactions and the deaths of at least 80 Americans. In that case, the active ingredient was manufactured in China. Thanks to the excellent work of the Subcommittee on Oversight and Investigations in 2008, we know that this is not a unique situation: the U.S. drug supply is increasingly sourced from abroad.

In order to market a drug in the United States, FDA must ensure that the drug meets our appropriately high safety standards. So when ingredients or finished drug products are manufactured abroad, FDA needs to expand its reach if the agency is to meet its responsibilities.

As heparin illustrated, FDA clearly needs more authorities and more resources to do a better job policing the safety of imported products. But what heparin also demonstrated is that we cannot expect FDA alone to do this job. We need to place a greater onus on all manufacturers to oversee the safety of their own products. This principle is reflected in the work that Mr. Dingell, Mr. Pallone and Mr. Stupak did on their Food and Drug Administration Globalization Act. For instance, the bill would require drug manufacturers to implement Quality Risk Management Plans to incorporate risk identification and control into their production processes. We need that.

This is a principle that should be familiar to all of us. The Food Safety Enhancement Act reflects this kind of approach with respect to food manufacturers. So I am confident we can get the same kind of bipartisan agreement to incorporate this concept into a bill on drug safety as well.

I hope FDA will tell us today about what the agency believes it needs to protect us from another heparin disaster.

I am also eager to hear about FDA's implementation of the 2007 FDA Amendments Act. Congress made some major strides toward improving the safety of our drug supply in enacting this legislation. For the first time, FDA was given the authority to require manufacturers, among other things, to conduct post-market studies, implement Risk Evaluation and Mitigation Strategies, or REMS, and make safety-related drug labeling changes. This hearing will be a great opportunity to learn about FDA's challenges and successes with the use of these authorities 3 years after the enactment of this landmark legislation.

I want to thank Dr. Sharfstein for being here. He is no stranger to me. We worked together in the past in the Oversight and Government Reform Committee and on many of these very same issues, and I am quite pleased that you are here and feel a sense of confidence that you are responding to us on these issues because I know you share our concern about them.

Thank you very much, Mr. Chairman.

[The prepared statement of Mr. Waxman follows:]

**Energy and Commerce Committee
Subcommittee on Health
Statement of Chairman Henry A. Waxman
Hearing on “Drug Safety: An Update from FDA”
March 10, 2010**

Thank you, Chairman Pallone, for holding this hearing today and giving us the opportunity to hear from the FDA on the critically important issue of drug safety.

Although it has been some time since the Committee focused on drug safety, that pause does not represent any lessening of our collective commitment to this issue. When we took up the food safety bill last year, we made it clear that the legislation was just a first step. As the Senate prepares to take up its version of the food safety legislation passed by the House last July, we turn next to drug, medical device, and cosmetic safety issues. We start that process with today’s hearing – knowing already that there is much work to be done in the area of drug safety.

We cannot forget the lessons of the 2007 heparin contamination catastrophe which resulted in numerous severe allergic reactions and the deaths of at least 80 Americans. In that case, the active ingredient was manufactured in China. Thanks to the excellent work of the Subcommittee on Oversight and Investigations in 2008, we know that this is not a unique situation: the U.S. drug supply is increasingly sourced from abroad.

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I want to thank Dr. Sharfstein for being here today and look forward to his testimony.

Mr. PALLONE. Thank you, Chairman Waxman.
Next is our ranking member, Mr. Barton.

**OPENING STATEMENT OF HON. JOE BARTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BARTON. Thank you, Chairman Pallone. We appreciate this hearing today. We appreciate our witness from the FDA coming.

Before I give my brief statement on the merits of the issue, I do want to reiterate the importance I place on this subcommittee and the importance I place on Mr. Shimkus assuming the ranking membership. On the Republican side, we have a bidding system for subcommittees where each member gets to rank one, two, three their preference for subcommittees. The most sought-after subcommittee on the Republican side of the full committee is the Health Subcommittee, as it should be, given the size of the health issue in our debates here in the Congress. Congressman Deal has done an outstanding job, first as subcommittee chairman and the last two terms as ranking member but he is pursuing the governorship in Georgia, so I thought long and hard about who to replace him with, and Mr. Shimkus is somebody who has paid his dues. He has an almost 100 percent attendance record as a member of this subcommittee. He also serves on two other subcommittees and his attendance record there is excellent. He gets into the details of the issues, and while any member of the subcommittee on the Republican side I think would make an excellent ranking member, I feel Mr. Shimkus will not have a learning curve, so I welcome him to his new duties and I hope that he conveys to them the same sense of excellence he has in all the other duties he has assumed on the committee.

With regard to today's hearing, it is good to review what we have done with the bill that we passed in the last Congress. We are especially interested on the minority side, as has already been outlined, the REMS issue, the Risk Evaluation Mitigation, how that is working. We also would be interested in hearing about the new rules that we put into statute regarding conflict of interest and how those rules are being used. We hear some concern that it has become difficult to get the experts needed on these review panels because of the conflict-of-interest rules that we have adopted, so we want to hear about that.

As Chairman Waxman has pointed out, there is hope that we can work in a bipartisan fashion on future FDA reform measures. Chairman Dingell and I are working on that very issue at the staff level, and we are hopeful that our friends on the majority side will adopt the model of bipartisanship that they exhibited in the last Congress and in this Congress so far with the FDA and not the model of partisanship that they adopted on the larger comprehensive health reform bill. I think the proof is in the pudding. When we work together in a bipartisan fashion, we certainly have differences but we end up with bills that pass committee with almost unanimous support and bills that pass the floor with over 400 votes. When the other route is chosen, we have bills that barely pass committee and barely pass the floor and as of now there doesn't appear to be a compromise between the House and the Senate and the President that can pass anywhere.

So we look forward to your testimony, and again, Chairman Pallone and Chairman Waxman, thank you for this hearing.
[The prepared statement of Mr. Barton follows:]

STATEMENT OF THE HONORABLE JOE BARTON
RANKING MEMBER COMMITTEE ON ENERGY AND
COMMERCE

HEALTH SUBCOMMITTEE HEARING:
“Drug Safety: An Update from the FDA.”
March 10, 2010

Mr. Chairman, thank you for holding this hearing today. Before we get into the substance of today’s hearing, I want to take notice of the starkly different ways in which we have handled two important health issues.

Almost three years ago, this Committee began the process to reauthorize several expiring FDA user-fee programs. Republicans were presented with a draft that was controversial and lacked any input from us. But there was real bipartisan interest in advancing legislation, and we

worked hard to bridge our policy differences. We ended up writing the Food and Drug Administration Amendments Act of 2007. That bill passed by a unanimous vote here and then it amassed more than 400 votes on the House floor.

That story started poorly and ended well.

Interestingly, we are replaying a similar story here in the House right now, but without the happy ending. Instead, the President and his majority party are going to pass a government takeover of health care that they created. We've witnessed a year's worth of showboating and theatrics, but it seems plain that Democrats have been, and still are, deaf to nearly every idea that diverges from the ones with a White House stamp of approval.

Now we're at a point where a complex budget process is going to be used to advance the president's will after the House passes the Senate health reform bill. I'd just like to point out that, as far as I know, this Committee has not marked up any legislation despite a specific requirement for us to do so in the budget's reconciliation instructions. I know that won't matter to many, but unless we are satisfied to function as White House servants, it better matter to us.

I also recognize that the White House threw reason off the train last year, but I want to make an appeal before the engine crashes into the public and wrecks health care for a lot of innocent people. There's still a moment or two left in which the brakes can be applied. I urge the leaders of this Committee to ask the President and Speaker Pelosi to stop

this raw, partisan bill that the American people have rejected again and again. Let us have the kind of normal, bipartisan discussions that can lead to consensus reforms. More than anyone else in Congress, the members of this Committee know how to do it because we have done it so often in the past.

Now, turning to the Food and Drug Administration Amendments Act of 2007, there was great debate and considerable thought given to the new powers granted to the FDA. I am interested in hearing from Dr. Sharfstein on how the FDA has approached and implemented these new authorities.

Specifically, I am interested in the decision-making process undertaken by the FDA to determine whether a

drug should have a Risk Evaluation and Mitigation Strategy, otherwise known as a REMS. The REMS process was a critical component of the drug safety reforms implemented in 2007. The FDA has used the REMS process to require a number of drug manufacturers to provide medication guides with their prescription drugs. Medication guides can provide useful information to patients. However, we must ensure the information being given to consumers is both useful and being read.

I am also interested in hearing about how the FDA is adapting to the new rules restricting conflict of interest waivers for advisory committees. In 2007, Members on both sides of the aisle cautioned that these new restrictions could actually have adverse consequences because the agency would find it difficult to fill slots on advisory

committees with knowledgeable individuals. While it is important that these advisory committees be independent, they must be filled with actual experts in the field to be effective. There have been news reports over the past year indicating a difficulty in filling advisory committee positions due to the onerous new rules, and I am eager to hear from Dr. Sharfstein on this subject.

I yield back the balance of my time.

Mr. PALLONE. Thank you, Mr. Barton.

Next is the chairman emeritus, and I should say that Mr. Dingell, as many of you know, has had a long history of working on this legislation or the issue of drug safety and food safety and is the prime sponsor of the bill that we have been operating on for the last couple of sessions on the topic. Thank you, Mr. Chairman.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Thank you, Mr. Chairman, for those kind words and I wish to commend you for having this hearing. It is a very valuable event and it will provide us an opportunity not only to receive and update information on drug safety activities at the Food and Drug Administration but also to remind the American people of the hazards which exist with regard to unsafe food and drugs and the fact that this Congress needs to move forward with legislation to address problems in both of these areas.

As you know, Mr. Chairman, we have reported from this committee a food safety bill which has passed the House. It came unanimously out of this committee and it has passed the House by an overwhelming vote. It sits, of course, safely ensconced in the United States Senate as these things usually do. We are hopeful that this hearing might trigger some interest in the Senate in this matter so that they can commence to go forward.

I want to commend my friend Mr. Barton for his comments with regard to food safety and safety of pharmaceuticals. As you know, Mr. Chairman, you, Mr. Stupak and I and Ms. Sutton and Ms. DeGette sponsor H.R. 759, which is a very significant improvement in all the things at Food and Drug including their authorities to address drug problems, food problems and also importation problems that deal with the importation at the point of import and to see to it that inspections at home and abroad and as well as that that good manufacturing practices obtained abroad, and I want to observe that Mr. Barton worked very well with us on that and that my Republican colleagues and my Democratic colleagues and I will work well to get that bill out of here and through the House.

I am hopeful that we can do something similar on the remnants of the legislation which we have passed which was H.R. 759. We received technical comments from the Food and Drug Administration and we believe that those are very helpful and will be incorporated. As my colleague Mr. Barton has observed, his staff and mine are working to see to it that we can bring together a bill which can achieve the support of my colleagues on the committee, and I look forward to the enthusiastic support in this subcommittee and in the full committee, and of course, I look forward to the help of Food and Drug and the Department of HHS as well as the Administration.

According to a 2004 HHS report, the Nation's medicine cabinets are still stuffed with enormous amounts of pharmaceuticals. Almost half of all people in this country take at least one prescription medicine and one in six has three or more medications that they take. Americans have come to expect that their prescription drugs will improve health and prolong life expectancy. They do not expect

their drugs to cause harm or death. The Food and Drug Administration plays a critical role in ensuring the Nation's drug supply meets the safety expectations of American consumers. The role FDA plays is so critical that it has earned that agency an American Food and Pharmaceutical Products as the gold standard not only of regulatory bodies but as regulatory substances.

Unfortunately, FDA approval of pharmaceuticals as a gold standard is now called into question by an unfortunate series of facts. Drug safety incidents have occurred and have created a confidence crisis in FDA. During the past 8 years, Food and Drug was led by leadership specialized at best in gross incompetence or at worst severe deception, and as a result, American lives have been placed in jeopardy under all the products that are marketed under the regulation of that agency, and of course, the confidence of the American people in that agency has been severely compromised.

Now under a new Administration, Food and Drug has been taking steps to rebuild, and through Congressional and administrative action, the agency has gained additional resources, not sufficient but to begin enabling it to move towards doing its job properly though many including myself still believe that the resources and authorities of Food and Drug are still lacking in the wake of years of inattention and starvation.

In 2007, the Congress made substantial progress in the way of drug safety with the passage of FDA Amendments Act of 2007. This law strengthened FDA's post-market safety oversight. No longer is it ok for the oversight to end at the mere approval of a drug. This is a significant step forward. However, it did not take long before we were aware of enormous gaps in FDA's ability to protect consumers from an increasingly global drug supply. In 2008, in one instance alone, 81 deaths of Americans were linked to recalled heparin that contained Chinese tainted API. The safety of imported pharmaceuticals and supplies as well as the raw materials from which these are made is a matter of safety and great concern that must be addressed in this Congress. Last year the Congress unanimously passed the bipartisan bill I mentioned with regard to our food safety supply. I believe that we can and should and will pass similar legislation during this Congress.

I look forward to the deputy commissioner's testimony. I hope he is able to give us better testimony than the predecessor of the current head of FDA gave us when he came up to tell us that all was well and to leave a patch of skin behind in this committee because of the unfortunate character of his testimony and his lack of information.

Mr. Chairman, I thank you again and I yield the balance of my time.

Mr. PALLONE. Thank you, Chairman Dingell.

The gentleman from Indiana, Mr. Buyer.

OPENING STATEMENT OF HON. STEVE BUYER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF INDIANA

Mr. BUYER. Thank you very much.

For the past several years, I have been studying the problem of counterfeit drugs entering our Nation through our 12 international mail facilities and express carrier facilities. In 2008, Congress

Matheson and I introduced the Safeguarding America's Pharmaceuticals Act to combat the flow of unapproved drugs into our country and to strengthen and safeguard the domestic pharmaceutical supply by creating also this system of electronic pedigree. At the beginning of last year when we introduced the legislation, we then submitted to the FDA and other stakeholders, Customs Border Protection and the California Board of Pharmacy to improve the Safeguarding America's Pharmaceuticals Act. I would ask you to look over your left shoulder because there are two ladies that were a lot of help. They put in a lot of time for the technical assistant. Elisa Bernstein, thank you very much. We traveled to many of these facilities with you. And Jeannie Ireland, thank you very much for the technical assistance you have given to make this legislation even better. Mr. Matheson and I have the commitment of Mr. Dingell and we want to make sure that this legislation becomes a reality.

Last June, Dr. Hamburg testified before this subcommittee and stated that the problem of counterfeit drugs is a significant concern and gave her commitment to working with me to address the issue, so I turn ask for the very same commitment.

The FDA then followed up in its response to many questions for the record and confirmed that the agency supports a single national uniform standard for a drug track and trade system. Additionally, the agency addressed an issue of great importance to me when it stated that it supports streamlining the destruction of these unapproved FDA drugs that constantly come into the market. And let us stop enabling these counterfeiters by this policy of return to sender. It is just awful, and I hope that you can address that to us. The worldwide counterfeit drug market is expected to grow to \$75 billion, so we have to aggressively address this, and I look forward to working with Mr. Dingell to do that.

So I know this is a great concern to you, and I look forward to working with you and your comments. I yield back.

Mr. FALLONE. Thank you, Mr. Buyer.

Next is the gentlewoman from the Virgin Islands, Mrs. Christensen.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman. I am waiving my opening statement.

Mr. FALLONE. Thank you.

The gentleman from Georgia, Mr. Gingrey.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, before I start, let me join with my ranking member on congratulating Mr. Shimkus as ranking member of this Health Subcommittee.

Mr. Chairman, first I would like to thank you for calling this hearing today. Ensuring that medications are both safe and effective for our Nation's patients is a goal that I believe we can all support. Whether our inquiries include pre-market and post-market testing of products, domestic and foreign facility inspections or even the authority and resources of the FDA, this committee and its chairman should be commended for their efforts today.

However, I want to focus for a moment on some troubling news that just came out of Britain. As some of you may have read earlier this week, the U.K.'s National Health Service received four independent audits on the overall state of their health care system. All four reports found a system that put the politics of the government above the health of the patient. One report based on the evidence of almost 200 top managers and doctors in the British system found that hospitals ignored basic hygiene so they could cram patients into beds to meet waiting time targets, thereby losing sight of fundamental hygiene requirements for infection prevention. This neglect of the most basic hygienic standards was credited with causing the deaths of 265 patients in 2005. All four reports in fact hit the same note: the British system placed little emphasis on patient care. Even more shocking, these reports are suppressed by the British government and only came to light recently. To quote the Times of London, "These reports diagnose a blind pursuit of political and managerial targets as the root cause of a string of hospital scandals that have cost thousands of lives."

I see the same blind pursuit of political targets in our current health care reform debate. For the past week, I have seen the demonization of the insurance industry. Sure, the industry needs reform. We all agree with that. But insurance reforms alone should not be the reason for turning health care over to our government lock, stock and barrel, and if the Senate bill passes, what then? Who is going to monitor our government when it controls all health care decisions? If the British are our example, will politics supersede the needs of patients here like they did in the U.K.? I fear that Washington politics have already trumped their needs. Our constituents are telling us that they want reform but not this reform. They don't want a bill bought with political payoffs and back-room deals. Every day they echo these sentiments, yet their elected officials ignore them. They voted for a Republican to represent Massachusetts in the United States Senate and still Washington refuses to listen. If we cannot trust our government to put its citizens first when debating a health care reform bill, how can we expect it to safeguard their citizens' interests when it controls health care? If Britain continues to be our example, I fear for the safety of patients if our government controls our health care choices.

Mr. Chairman, with that I yield back.

Mr. PALLONE. Thank you.

Next is the gentleman from Iowa, Mr. Braley.

**OPENING STATEMENT OF HON. BRUCE L. BRALEY, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF IOWA**

Mr. BRALEY. Thank you, Mr. Chairman. I am very pleased that we are holding this important hearing and I am very pleased with the scope of the testimony that Dr. Sharfstein has laid out in his written materials.

I want to begin my brief remarks by echoing the concern raised by my colleague from Indiana, Mr. Buyer, because one of the things that was very obvious to me when I visited the Custom and Border Patrol inspection facilities in Nogales, Arizona, and Mexico, is that we have an enormous problem with counterfeit drugs entering through ports of access and other places that are not being con-

trolled, which contributes enormously to the problem you have identified with the known points of products for non-counterfeit drugs. So we have got two major problems in terms of enforceability of the FDA's mandate in counterfeit and non-counterfeit production facilities overseas. We also have enormous challenges in terms of the accountability of the manufacturers of those non-counterfeit and counterfeit drugs in this country, and one of the things that I hope you are able to address in your testimony is what the FDA is doing to promote greater accountability with those overseas manufacturers.

I also want to compliment you on some of the progress has been made since the passage of the FDAAA because I personally benefited from one of the changes you identified in your statement where you describe the changes to the prescription information of a class of antibiotics to warn about the risk of tendon rupture. I have experienced a ruptured Achilles tendon, and when I was prescribed those antibiotics, as a patient I was given informed information to make a choice about whether or not to take that antibiotic in light of my own health history. So I can tell you that if consumers are presented with information that allows them to make the choices that are best for them based upon their own unique health conditions, the FDA is fulfilling the mandate that you set forth so succinctly at the beginning of your written remarks.

But I also want to hear from you in your testimony about the Sentinel Initiative that you described, which you have identified as a national integrated electronic system for monitoring medical product safety. The concern I want you to address is exactly what model that Sentinel Initiative is based upon because I am familiar with other sentinel event reporting systems that have been adapted in this country designed to promote patient safety that have been woefully inadequate in reaching the level of reporting that would be required to truly bring about changes in patient safety.

So I look forward to your comments. I appreciate your willingness to come here today. It is a very important subject that affects every American, and this is not a partisan issue, it is a bipartisan issue that every American should be concerned about, and I yield back.

Mr. PALLONE. Thank you, Mr. Braley.

The gentlewoman from Tennessee, Mrs. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman.

I am so pleased that we are doing an oversight hearing today. Oversight is something that we should doing a little bit more of, and I think that after we passed the FDA Amendments Act in 2007 that was supposed to help streamline some of those processes and procedures that it is important that we come back and look at what is happening with the efficiencies in this area as well as to look at the relationship between the FDA and industry, and some of my colleagues have mentioned some of the conflict-of-interest questions that we will have.

I also hope that today we are going to look at whether or not the FDA has the appropriate resources as well as the institutional will to continue to evolve and review processes that are in place, and I know, Dr. Sharfstein, that you are very well aware that with the inspections process with NDA and ANDA, we hear from constituents who may have questions or concerns as they have gone through that process. So I think that is something we need to jointly look at to see is this review process working and how do we simplify it, how do we look at time, money, the usage as well as public safety. So I thank you for your willingness to look at that.

The other point that I hope we look to is FDA's internal problems and see if those have improved not only with the decision-making process but also the oversight and the post-market drug safety issues that are out there, the counterfeit, and then let us also touch on one of the things we have talked about repeatedly over the last few years which is your interagency communications and the different divisions and how they are transferring that information. Repeatedly we have seen this as a roadblock or being cited as well we didn't know they were doing. So I hope that you will take a moment to address that.

I thank you for being here with us. We welcome you.

Mr. Chairman, I yield back.

Mr. PALLONE. Thank you, Mrs. Blackburn.

And next, the gentlewoman from California, Ms. Eshoo.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Thank you, Mr. Chairman. This is an important hearing, and I thank you for having it.

Before the FDA was created about a century ago, taking drugs was a real gamble. There were elixir potions that were sold door to door and "medicines" were really taken at one's own risk. Today, as was stated previously and we all know, there are millions of Americans that take drugs to prevent, to treat and to cure ailments from the common cold to cancer, and the science and technology progresses and I see every day the new things that surface in my Congressional district and certainly around the country, so do the complexity of drugs as well as our ability to regulate them and ensure their safety. So I think that the FDA is the gold standard in the world and I think that we all want the FDA to remain the gold standard in the world. The recent heparin incident was a stark example of what happens when that standard is not followed and it cost 81 American lives. Lapses in drug safety not only harm patients but they cause the public, and I think this is really an important outcome of this, it causes the public to doubt the government's ability to actually ensure safety. So we have to maintain the trust and the support of the American people who rely on safe and effective drugs.

I am very pleased to see Dr. Sharfstein here today. I would like to know about how the FDA is implementing two provisions that I offered in the Food and Drug Administration Amendments Act to renew and improve the Best Pharmaceuticals for Children Act, the BPCA, and the Pediatric Research Equity Act, PREA. The provi-

sions, as you know, were designed to improve drug safety for children in two ways. First, under the BPCA, the legislation provided an incentive for a drug of the innovator company agrees to undertake comprehensive pediatric studies requested by the FDA, and second, under PREA, the FDA was granted the authority to require studies when there is a demonstrated need and the drug companies are required to submit a pediatric assessment. I am telling you what you already know.

So my thanks to Dr. Sharfstein for being here today. I look forward to your testimony. I want to thank everyone that is part of helping to keep FDA as the gold standard in the world and to work with you and make sure that we provide the resource that you need in order to do that and good public policy to back it up.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you.

Next is the gentleman from Pennsylvania, Mr. Pitts.

Mr. PITTS. I will waive.

Mr. PALLONE. Thank you.

The gentleman from Georgia, Mr. Barrow.

Mr. BARROW. Thank you. I will waive.

Mr. PALLONE. The gentleman from Kentucky, Mr. Whitfield.

Mr. WHITFIELD. Thank you, Chairman Pallone, and I also want to congratulate Mr. Shimkus on his new responsibilities of this subcommittee, and Dr. Sharfstein, we are delighted you are here to bring us up to date on the implementation of this act of 2007.

People have already touched on a lot of these issues, the safety of drugs coming into the country, the approval process, whether or not there are adequate resources, and I just want to point out one additional aspect of this, which is a little bit different, but this committee a couple years ago passed the National Prescription Drug Monitoring System which I think is vitally important to health care providers. We continue to struggle on getting sufficient funds to fully implement this because of an unauthorized program started in the Appropriations Committee but we have been working with both sides of the aisle to try to address that issue and I certainly look forward to your testimony on the other part of this equation. Thank you.

Mr. PALLONE. Thank you, Mr. Whitfield.

The gentleman from Connecticut, Mr. Murphy. Well, Mr. Green just walked in. Do you want to go first? Mr. Green.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. I would like to put my full statement into the record.

Following our chairman emeritus and the earlier statements, first I want to thank you for holding the hearing and today with new FDA folks on the current status of our drug safety system, and a lot of our frustrated that the Senate hasn't moved on the bill but I had the opportunity like a lot of members on several hearings led by Chairman Pallone and Chairman Stupak, the FDA and drug safety over the past 2 years. All these hearings clearly show the FDA is woefully underfunded and neglected by Congress for far too many years and that has left the FDA without the resources, funding or technology it needs to protect the American public from

counterfeit or tainted drugs entering our country. This committee worked over a year on FDA drug safety legislation passed out of the committee. The legislation is aimed at improving our drug safety system by giving FDA increased resources for overseeing facility inspections by the FDA, an up-to-date registry of all foreign drug manufacturing facilities, country-of-origin labeling, verification of drug purity and safety. It gives the FDA the ability to issue fines and mandatory recalls, and also the FDA's foreign drug inspection program needs to be changed and some hurdles to overcome. The FDA currently does not have the authority to conduct these inspections overseas and must be invited to a plant to conduct inspections. That is almost like me driving down the Houston freeway inviting an officer to watch me while I speed. That just doesn't work in the real world.

And Mr. Chairman, that is why I would hope with the new FDA that they will not only take their job seriously, and I know they do, but also we need to provide the resources for them, and I appreciate the opportunity to give the opening statement and again, I would like to have my full statement placed in the record.

[The prepared statement of Mr. Green follows:]

**Statement of Congressman Gene Green
Committee on Energy and Commerce
Subcommittee on Health
Drug Safety: An Update from Food and Drug Administration
March 10, 2010**

Mr. Chairman, I want to thank you for holding this hearing today with the new FDA folks on the current status of our drug safety system.

I had the opportunity to participate in several hearings led by Chairman Pallone and Chairman Stupak the FDA and drug safety over the past two years.

All of these hearings clearly show that the FDA has been woefully underfunded and neglected by Congress for far too many years.

This has left the FDA without the resources, funding, or technology it needs to protect the American public from counterfeit or tainted drugs entering this country.

This Committee worked for over a year on drug FDA drug safety legislation and passed it out of the Committee.

This legislation aimed to improve our drug safety system by giving the FDA increased resources for overseas facility inspections by the FDA, an up to date registry of all foreign drug manufacturing facilities, country of origin labeling, verification of drug purity and safety, and gives the FDA the ability to issue fines and mandatory recalls.

Also, the FDA foreign drug inspection program needs to be changed and has some hurdles to overcome.

The FDA currently does not have the authority to conduct inspections at will overseas and must be invited to a plant in order to conduct inspections and the FDA often warns plant officials before they are inspected.

Additionally, the FDA does not rely on end product testing with drugs as they do with food products, which can detect contamination in a final product. Also, the FDA does not have one system to track and monitor foreign drug inspections.

The FDA needs resources including more employees, an IT system, and appropriate funding. In short, the foreign drug inspection program needs a complete overhaul in order to ensure product safety, which I know is something we all want.

We passed the Food Safety Enhancement Act out of the House and I am hopeful we will begin work on drug safety and the FDA soon.

Additionally, I've been a strong supporter and original cosponsor of legislation, Safeguarding America's Pharmaceuticals Act, which was proposed in the 110th Congress by Reps. Buyer, Matheson, and Rogers.

This proposed legislation makes changes to help protect our nation's pharmaceutical supply as well.

The proposed Safeguarding America's Pharmaceuticals Act also gives us one national pedigree system to allow for consistency and efficiency when pharmaceuticals are moving about the country.

The bill also creates a track and trace system, that will establish a drug identification and tracking system through which drug manufacturers, repackagers, wholesale distributors, and dispensers may authenticate the wholesale distribution history of any prescription drug that has the standardized numerical identifier.

Again, I want to thank the Chairman for holding this hearing today and I want to thank the witnesses for appearing before the committee today. I yield back my time.

Mr. PALLONE. Without objection, so ordered.

The gentleman from Texas, Mr. Burgess.

Dr. BURGESS. Thank you, Mr. Chairman. I will waive opening statement and reserve time for questions. Welcome, Dr. Sharfstein, to our committee.

Mr. PALLONE. Thank you.

The gentleman from Connecticut, Mr. Murphy.

Mr. MURPHY OF CONNECTICUT. Thank you, Mr. Chairman, and welcome, Dr. Sharfstein.

In your testimony, you recite some of the examples of safety lapses that we have seen and you summarize by saying, "These episodes and others are not random mistakes, they are driven by a common feature, which is economic incentive." And I guess it underscores what we have seen as a facet of our health care system for a very long time. Too often, profit is being put ahead of quality and safety, and everything we do, whether it is changing the way that the FDA works or whether it is the discussion surrounding health care reform, has to be around reversing that phenomenon. We have to be putting safety and quality first, profit and cash second whether it is running the FDA, whether it is how we reimburse providers or whether it is how we regulate insurers. I don't begrudge drug companies from making a buck. We have got a lot of very good ones in Connecticut. But we should never, ever be sacrificing safety for profit. We should never, ever be sacrificing quality for profit. That I think is the guiding principle behind health care reform and that of course I know is the principle that you bring to your leadership at the FDA, and I appreciate your testimony today.

Mr. PALLONE. Thank you. The other Mr. Murphy from Pennsylvania.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman.

I would first like to mention, unfortunately I am not going to be able to remain here, Chairman and Dr. Sharfstein, although I would love to hear your testimony. You know what it is like, we have other things pending.

But I would like to bring something to your attention in this, and if it not something you are able to respond to today, please, I hope you can get back to me. I wanted to tell you about a couple of my constituents, Russell and Robely Rosewitz in Mount Lebanon. They have lived a terrible tragedy. Their daughter, Hannah, was vaccinated for DPT, as you know, diphtheria, pertussis and tetanus, and 2 hours after she received her shot, she began experiencing seizures. She was once a healthy infant and now she needs 100 percent round-the-clock care. Unfortunately, adverse reactions to complicated vaccines do occur and years upon years of scientific evidence have shown the public health benefits of vaccination are greater than the isolated, unfortunate adverse action. And to encourage families to vaccinate their children and ensure vaccine makers continue produce lifesaving medicine, Congress passed the National Childhood Vaccine Injury Act in 1986. This law compensates

victims of vaccination adverse effects and allows the Secretary of Health and Human Services to automatically award damages when a victim has experienced adverse reactions. But the DPT vaccine in this case was removed from the table of vaccines known to cause adverse events just 1 month prior to when Hannah's family applied for compensation. After a 10-year legal battle to prove that the vaccine caused Hannah's seizures, the case is now before the Supreme Court. Hannah's parents believe there were safer alternatives to the DPT vaccine administered to their daughter. The question before the Supreme Court is whether or not companies are immune to civil suits if they participate in vaccine victims' compensation fund.

Now, I am not here to argue the merits of the case. The Supreme Court will decide whether or not that was the Congressional intent. But this case raises an important issue about vaccine safety. For example, if they are imported and the FDA is not capable of inspecting the manufacturing process, then where does the responsibility and liability for assuring safety lie? By the way, that particular DPT vaccine was later removed from the market after 50 years of sales.

So I hope at some point you can get back to us and let us know about some of these important issues. I know you are deeply concerned as are we, and quite frankly, I believe that contrary to what some others may say, that manufacturers also want to ensure the safety of their products because they do not want to see anybody harmed from these as well. so if you could please get back to us and let us know how we keep up-to-date on the latest scientific evidence here and how you are ensuring vaccine makers are using the latest and safest innovation in vaccine design.

Thank you so much for being here. Again, I apologize. I wish I could stay because I am deeply interested in hearing your testimony, but I look forward to hearing from you.

And with that, I yield back, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Murphy.

The gentleman from Utah, Mr. Matheson.

**OPENING STATEMENT OF HON. JIM MATHESON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF UTAH**

Mr. MATHESON. Thank you, Mr. Chairman. I do appreciate this hearing and look forward to the testimony.

In the coming weeks, I will be introducing a bipartisan bill with my colleague, Representative Buyer, to develop a system for the protection of our Nation's pharmaceutical supplies for domestic and international counterfeiting threats. Within the past 2 years, Representative Buyer and I have engaged stakeholders all along the supply chain to develop a workable and commonsense approach. As an integral part of the stakeholder process, I also appreciate the recent helpful comments from the Food and Drug Administration and their suggestions of how to improve upon our approach and achieve our shared ultimate goal.

Specifically, core elements of the bill that we plan in introducing are the creation of a system by which we will be able to track drugs from the time they leave the manufacturing facility to the time they reach patients in the pharmacy, hospital, nursing home or

doctor's office. Counterfeiting of drugs is a public health concern. By implementing these steps now, we can go a long way towards safeguarding the medicine people need to get well and stay healthy.

Another feature will be one uniform national pedigree system. By having one federal standard, I believe we can ensure our Nation's drug market is efficient, it can ensure products flow safely and freely throughout the country. This is a guiding principle that seems to unite a majority of the members of the supply chain.

Third, our bill will raise the standards for drug wholesalers while maintaining States' rights to regulate drug wholesalers. I believe this is a necessary step to ridding the market of bad actors and ensuring that anyone handling America's pharmaceuticals must be held to high standards.

Counterfeit drugs are the latest and potentially the most dangerous front in the long-running battle against intellectual-property crimes. In 2007, pharmaceuticals made up about 6 percent of total seizures. Last year they accounted for 10 percent to become the third largest category with an estimated market value of \$28 million. Counterfeiters are alarmingly good at their jobs. They can create pills and drug packages that are so close to real products that they are indistinguishable to consumers. By strengthening current laws and regulations, building upon the successful model signed into law in California, and by creating a uniform national standard, our legislation further secures the health care supply chain. This enhances our country's and the Food and Drug Administration's high standard for patient safety.

I look forward to the witness testimony. I will yield back my time.

Mr. PALLONE. Thank you.

The gentlewoman from Colorado, Ms. DeGette.

Ms. DEGETTE. I will submit my statement for the record.

[The prepared statement of Ms. DeGette was unavailable at the time of printing.]

Mr. PALLONE. Without objection, so ordered.

I think that that concludes our opening statements by members of the subcommittee, so we will now turn to our one witness, which we are so pleased that Joshua M. Sharfstein is here today. He is the principal deputy commissioner from the Food and Drug Administration, and thanks for being here, or coming back to us, so if you would give us your statement, we would appreciate it.

STATEMENT OF JOSHUA M. SHARFSTEIN, M.D., PRINCIPAL DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION

Dr. SHARFSTEIN. I thank you very much. It is good to be back here. Good afternoon, Mr. Chairman and members of the subcommittee. I am Dr. Joshua Sharfstein, the principal deputy commissioner at the Food and Drug Administration. Thank you for the opportunity to discuss the safety of the U.S. drug supply.

Protecting Americans from unsafe or contaminated drugs is not just an important responsibility of FDA, it is our core charge. Drug safety was the primary reason for the passage of our guiding statute. In 1937, more than 100 people, including many children, died from ingesting Elixir Sulfanilamide, which contained the deadly

poison diethylene glycol. Congress then passed, and President Franklin D. Roosevelt signed, the Food, Drug, and Cosmetic Act to prevent future catastrophes. And yet as you know, many years later, the threat of unsafe drugs remains.

I would like to thank the subcommittee for its leadership on this issue twice. First, thank you. There have been numerous hearings in this chamber have helped the public understand the challenge of regulating a global marketplace. And second, members of this subcommittee, along with the chairman of the full committee and the chairman emeritus, were the key architects of the Food and Drug Administration Amendments Act of 2007, which gave the agency significant new authorities and resources to address the safety of drugs. In this testimony, I will cover both of these important issues: import safety and the implementation of the drug safety authorities in what we call FDAAA.

Globalization has created new risks and challenges for the safety of the drug supply. Where Americans once used drugs that were mostly manufactured domestically, now up to 40 percent of the drugs we take are imported, and up to 80 percent of the active pharmaceutical ingredients in these drugs are from foreign sources. This makes oversight significantly more difficult and leads to weaknesses through which counterfeit, adulterated and misbranded products can infiltrate the legitimate supply chain. That was the case with the contamination of heparin in 2007 and 2008 and most recently with the counterfeit Tamiflu discovered during the H1N1 outbreak.

When the modern FDA was created in 1938, imports were a tiny part of the products used in our country. Now that an estimated 20 million shipments of FDA-regulated imports come into this country every year, FDA must adopt a new approach, one that addresses product safety by preventing problems at every point in the global supply chain from the raw ingredient through production and distribution all the way to U.S. consumers.

In the food arena, this approach to prevention is embodied in legislation passed by this subcommittee and the full House of Representatives, which is now awaiting action in the Senate. In the area of drugs and other medical products, we are taking a number of steps to begin making this shift as best we can with our current authorities. But there is much more to be done.

As Secretary of Health and Human Services Kathleen Sebelius noted when she appeared before this committee, FDA needs additional tools to move our oversight capabilities into the 21st century. FDA needs to access regulatory information quickly, hold all parties responsible for the quality of products in the supply chain and have reasonable and reliable options for enforcement.

I will now turn to the drug safety authorities in FDAAA, a milestone legislative achievement that has helped the agency protect the public health in many ways. FDAAA provided important new authorities to enhance our ability to monitor approved drugs after they are marketed and to take definitive action when needed. With our new authority, FDA has required drug sponsors to conduct around 200 post-marketing studies or trials. The agency has required safety-related labeling changes in individual or classes of drugs 32 times and has developed and put into place 10 evaluation

and mitigation strategies with elements to support safe use into the REMS, all with the goal of better identifying and managing the risk of drugs on the U.S. market.

To give you one example, FDA has established a program to support the safe use of a product, a medication in patients with a very severe bleeding disorder in which the blood does not clot because of low platelets. This medication, however, has serious side effects which include blood cancers, bone marrow fibrosis, a risk of blood clots, and even worse platelet counts when the therapy is stopped. However, it is an important treatment option for patients who have failed to respond to other therapies. By requiring elements to ensure safe use, the benefits of the drug can outweigh the risks and we can provide patients access to this critical product without being concerned that it would be used in other patients and could cause them more harm than good.

I also want to know that FDAAA also reauthorized and amended the Best Pharmaceuticals for Children Act, which continues to provide valuable safety and dosing information for the use of drugs in children. As a pediatrician, I echo the comments of Congresswoman Eshoo, who worked so hard on this issue. This legislation represents a fundamental shift in prescribing for the pediatric population, even since the passage of the FDAAA legislation, 109 labeling changes related to the use of medications in children. It has been a tremendous step forward for pediatrics. We are very happy to discuss the lessons we have learned over the last 2 years in implementing FDAAA and work together to fine-tune the program.

Over the last 7 decades, so much has changed in pharmaceutical science and drug regulation, yet in 2007, when scores of patients died from contamination of medications in Bangladesh, and in 2006 when children died in Panama, the culprit was familiar. It was diethylene glycol, the very same poison that had led to the passage of the Food, Drug and Cosmetic Act in 1938.

FDA's work is far from done. The scientists, doctors, nurses, inspectors and other public health professionals, some of whom are here with me today, who make up FDA thank you for your support for our mission.

I appreciate the opportunity to testify today and am happy to address any questions you may have.

[The prepared statement of Dr. Sharfstein follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STATEMENT OF

JOSHUA M. SHARFSTEIN, M.D.
PRINCIPAL DEPUTY COMMISSIONER
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

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

MARCH 10, 2010

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Joshua M. Sharfstein, Principal Deputy Commissioner at the Food and Drug Administration (FDA or the Agency) in the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss the safety of the American drug supply.

Protecting Americans from unsafe or contaminated drugs is not just an important responsibility of FDA—it is our core charge. Drug safety was the primary reason for the passage of our guiding statute. In 1937, more than 100 people, including many children, died from ingesting Elixir Sulfanilamide, which contained the deadly poison diethylene glycol. Congress then passed, and President Franklin D. Roosevelt signed, the Federal Food, Drug, and Cosmetic Act (FD&C Act) to prevent future catastrophes.

And yet, as you know, the threat remains.

I would like to thank the Subcommittee for its leadership on this issue. Numerous hearings in this chamber have helped the public understand the challenge of regulating a global marketplace. Members of this Subcommittee, along with the Chairman of the full Committee and the Chairman Emeritus, were key architects of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which gave the Agency significant new authorities and resources to address postmarket safety.

In this testimony, I will address two important issues: import safety and the implementation of the drug safety authorities in FDAAA.

IMPORTS

As the Subcommittee's work has documented, globalization has created new risks and challenges for the safety of the drug supply.

Where Americans once used drugs that were mostly manufactured domestically, now up to 40 percent of the drugs we take are imported, and up to 80 percent of the active pharmaceutical ingredients in the drugs we use are from foreign sources. In addition to the growth in the sheer volume of imports and foreign facilities, there has been an increase in the variety and complexity of imported products, and a large expansion in the number of countries involved in producing these products—including many with less sophisticated regulatory systems than our own. Simultaneously, the supply chain from raw material to consumer has become more and more complex, involving a web of repackagers and redistributors in a variety of locations. This makes oversight significantly more difficult and leaves weaknesses through which counterfeit, adulterated, and misbranded products might infiltrate the legitimate supply chain.

A few examples:

- In 2007 and 2008, contaminated heparin (a blood-thinning drug) came from China and was linked to deaths and a number of serious allergic-type reactions here at home.
- Counterfeit Tamiflu (oseltamivir phosphate) was discovered during the novel H1N1 outbreak.

- In 2007, Xenical (orlistat) capsules ordered over the Internet were found to be composed only of talc and starch.
- In January 2010, counterfeit Alli (orlistat) was discovered, which did not contain the active ingredient but instead contained varying amounts of the stimulant sibutramine, which can lead to serious toxicity if used by people with certain cardiac diseases.

These episodes and others were not random mistakes. They share a common feature—an economic incentive. In the case of heparin, it appears that a contaminant was introduced to increase the profit of the raw material suppliers. In the case of counterfeit drugs, criminals can make millions by pretending their dangerous or ineffective products are safe and effective. These are despicable acts that seek profit by putting lives at risk.

These are global problems. Contamination and counterfeit drugs represent a much greater threat in the developing world, where the systems of laws and regulatory oversight do not afford much protection. And these problems can pose a risk to us at home, when, for example, patients do not get fully treated for infection abroad because of ineffective drugs ... and as a result, drug resistance intensifies.

When the modern FDA was created in 1938, imports were a tiny part of the products used in our country. Our focus was on stopping harmful products at the border through inspections of imported goods. This approach is adequate to the challenge when the volume is small. But it fails when an estimated 20 million shipments of FDA-regulated imports come into the country each year.

To fulfill our public health mission in a global age, FDA must adopt a new approach—one that addresses product safety by preventing problems at every point along the global supply chain, from the raw ingredient through production and distribution, all the way to U.S. consumers.

We are moving from an approach based on reacting to problems to one that proactively prevents such problems from ever occurring.

In the food arena, this approach to prevention is embodied in legislation passed by this Committee and the full House of Representatives, and which is now awaiting action in the Senate. This bill would for the first time allow FDA to establish basic preventive controls throughout the food production process and give the Agency strong enforcement authorities and resources to meet these obligations.

In the arena of drugs and other medical products we are taking a number of steps to begin making this shift within our current authorities.

First, we are seeking better controls at the point of production, wherever that may be.

We now have permanent FDA offices in Beijing, Shanghai, and Guangzhou, China, in New Delhi and Mumbai, India, in San Jose, Costa Rica, Mexico City, Santiago, Chile, and soon, Amman, Jordan. These offices enable us to have a regional presence around the world, a home base from which to undertake a range of important activities, including building regulatory capacity.

We now have more than 30 agreements with foreign counterparts to share inspection reports and other nonpublic information that can help us make better decisions about the safety of foreign

products. So if a shipment of contaminated drugs shows up in a port in Italy, we will hear about it swiftly and be on the lookout for products from the same shipper.

Second, we are working with industry to help them strengthen the safety of their supply chains. In this day and age, companies should be able to effectively demonstrate that safety, quality, and compliance with international and U.S. standards are built into every component of every product and every step of the production process.

Some companies already do a terrific job at this, tracking where and how their products and their components are made and the path taken to reach our shores. In fact, I have met with some companies that react with incredible swiftness to questions about the integrity of their supply chain. Obviously they have a vital interest in ensuring confidence in the safety and quality of their products and their brand. These best practices need to become standard practice throughout industry.

There is much more to be done. As Secretary of Health and Human Services Kathleen Sebelius noted when she appeared before this Committee on February 4, 2010, FDA needs additional tools to move our oversight capabilities into the 21st century. FDA needs to access regulatory information quickly, hold all parties responsible for the quality of products in the supply chain, and have reasonable and reliable options for enforcement.

DRUG SAFETY AUTHORITIES IN FDAAA

I will now turn to the drug safety authorities in FDAAA, a milestone legislative achievement that has helped the Agency protect the public health in many different ways.

Because no amount of premarket study can provide the full information about what the benefits and risks of a new drug will be when it is used by the general population, FDAAA provided important new authorities to enhance our ability to monitor approved drugs after they are marketed and to take definitive action when needed.

Under FDAAA, FDA can require drug sponsors to conduct postmarketing studies and clinical trials, make certain safety-related labeling changes, and develop and put into place risk evaluation and mitigation strategies (REMS)—all with the goal of better identifying and managing the risks of drugs on the U.S. market.

Here are some details.

Between the passage of FDAAA and March 8, 2010, FDA has required that sponsors conduct around 200 postmarketing studies or trials. FDA is tracking the conduct of these studies and will take enforcement action if studies are not conducted in a timely manner without good cause.

With respect to label changes, as of February 28, 2009, FDA had used its new authorities to require safety label changes in individual or classes of drugs 32 times since March 25, 2008. For example, FDA required safety label changes to add the risk of a life-threatening neurological disorder to the prescribing information for certain antidepressants, and changes to the prescribing information of a class of antibiotics to warn about the risk of tendon rupture.

With respect to risk management, if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug, FDA can require manufacturers to have a REMS in place when a drug comes on the market, or implement one later if FDA becomes aware of new safety data. The authority to require REMS provides FDA a very useful set of tools that can be used to reduce the risks of marketed products, while allowing patients to benefit from lifesaving and other beneficial treatments that could not be safely marketed without a risk management program.

In the design of REMS with elements to ensure safe use (the most comprehensive REMS programs), FDA is mindful of the provisions in FDAAA stating that the elements to ensure safe use must be, among other things, commensurate with the specific serious risk listed in the FDA-approved labeling of the drug, not be unduly burdensome on patient access to the drug, and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

Most of the REMS with elements to ensure safe use include educating prescribers about the risks and appropriate use of the drug as a condition of certification or enrollment in the REMS program. Other programs require enrollment by pharmacists and sometimes patients as well. Some programs require the prescriber to monitor the patient immediately following drug administration and for a period of time afterwards. Each of these programs is designed to provide critical information to clinicians without unduly restricting access to the drugs.

We have learned that designing and implementing the most comprehensive REMS requires a careful balancing of the need to adequately manage risks and also to maintain patient access to important medications. Since using this authority is a work in progress, FDA is committed to addressing the concerns we have heard from prescribers, pharmacists, distributors, and payers about their roles in implementing REMs and from patient groups about the effects of REMS on access to needed products, and are planning to hold a public meeting to hear from these and other stakeholders.

Additional implementation challenges include ensuring consistency in the handling of safety problems with all products, including over-the-counter (OTC) products and generic drugs; the lack of clarity in certain provisions of the law with respect to REMS; and burdens imposed on application holders and FDA that do not contribute significantly to drug safety. We would be very happy to discuss the lessons we have learned over the last two years with Congress and work together to fine tune the program so that it can be even more effective in improving public health.

Sentinel Initiative

FDAAA requires the HHS Secretary to develop methods to obtain access to disparate data sources and to establish a postmarket risk identification and analysis system to link and analyze health care data from multiple sources. On May 22, 2008, FDA launched the Sentinel Initiative with the ultimate goal of creating and implementing the Sentinel System—a national, integrated, electronic system for monitoring medical product safety. The Sentinel System, once up and running, will enable FDA to actively gather information about the postmarket safety and

performance of its regulated products—a significant step forward from our current, primarily passive safety surveillance systems. The law sets a goal of access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012.

FDA has gathered public input on issues related to the creation and development of Sentinel, held numerous meetings and a public workshop, and established a working group consisting of representatives of numerous federal agencies to share information and discuss issues related to ongoing efforts that are complementary to Sentinel. FDA has awarded key contracts for a pilot project to gather information that will be essential to fully implementing the Sentinel System.

Track and Trace

FDAAA also required the development of standards for the identification, validation, authentication, and tracking and tracing of prescription drugs as a step towards further securing our nation's drug supply. Very shortly, FDA will issue a guidance establishing a standard for unique identification for prescription drug packages, which ultimately will help in identifying the whereabouts and authenticity of drug packages and distinguish them from counterfeits.

SAFE USE INITIATIVE

Before I close, I would like to briefly mention a new drug safety initiative at FDA called the Safe Use Initiative. Every approved drug has both benefits and risks. Underlying FDAAA is the principle that Congress wants to see the benefits maximized for patients and the risks minimized. We all want patients to get better on medication and avoid unnecessary injuries, even death, as a result of preventable medication errors or misuse.

In November 2009, we announced the launch of FDA's Safe Use Initiative. Through this initiative, FDA will identify, using a transparent and collaborative process, specific candidate cases (e.g., drugs, drug classes, and/or therapeutic situations) that are associated with significant amounts of preventable harm. FDA will then work with hospitals, doctors, nurses, patient groups and others to recognize and mitigate these risks. In a voluntary complement to the REMS program, we will use our understanding of drug risk as a tool to gather partners together and develop and implement strategies for progress.

CONCLUSION

Over the last seven decades, so much has changed in pharmaceutical science and drug regulation. Yet in 2007, when scores of patients died of contamination in Bangladesh, and in 2006 when children died in Panama, the culprit was familiar. It was diethylene glycol, or DEG—the very same poison that had led to the passage of the FD&C Act in 1938.

FDA's work is far from done. The scientists, doctors, nurses, inspectors, and other public health professionals who make up FDA thank you for your support and confidence in our mission.

Thank you very much for the opportunity to testify today. I welcome your ideas and your questions.

Mr. PALLONE. Thank you, Dr. Sharfstein. I appreciate your testimony. It is good. We are just going to have questions, as you know, alternating between the Ds and the Rs, and I will start out.

I mentioned in my opening statement that this committee worked very hard to pass the Food and Drug Administration Amendments Act of 2007. We call it FDAAA. And as part of FDAAA, Congress gave FDA the authority to require manufacturers to implement the so-called REMS, or Risk Evaluation Mitigation Strategies. They can require REMS when the agency believes it is necessary to ensure that a drug's benefits outweigh its risks. So I wanted to ask you initially, could you provide the committee with an update on how FDA has made use of this authority, how many REMS have been required and approved, and what has been the public health impact of REMS?

Dr. SHARFSTEIN. Sure. There are about 80 or 90 REMS that have been approved since the passage of the legislation. The vast majority of those are called medication guide only REMS where the REMS just consist of the fact that we have a medication guide for patients about the drug.

There are about 10 REMS for 10 drugs that have what we call elements to assure safety. This is sort of the next level of control, and that can include restrictions on which pharmacies can provide the medication, whether the doctor needs special training and whether there needs to be a patient registry, and these have been used for medications for seizures, for the low platelets that we were talking about before, for medications for schizophrenia, and they really make it possible for FDA to approve the treatment because without this ability to put some restrictions and some safeguards in place, we would be very worried that these medications could do more harm than good. I think that this is very clearly a work in progress.

There are certain things that in the implementation of this provision we have learned about. One of the issues is the differential treatment between generic medications and brand-name medications when it comes to communication plans. We can require that companies that make brand-name drugs do communication plans for health care professionals but when it comes to generic drugs, the FDA would have to pay for and run the communication plan.

So there are a few specific issues, and I am happy to talk about them more if you want, where we think that we could be more effective with REMS. One of the others is that we have the authority to require a REM but we don't necessarily have the authority to require a specific type of REM, so that leads to negotiations that can go on for a while between the company and FDA, and recently we did a REMS for certain medications that can stimulate the bone marrow that took, you know, over a year to develop.

So I think that there are definitely areas where this could be improved but in general our view is that this is a tremendously important authority and we are really making a lot of progress with it.

Mr. PALLONE. Well, I want to use an example of a drug that came to my attention, and I heard you say you have the authority to require REMS but not a particular type, and I would like you to comment on that. But let me throw this example out and then

I don't know if this relates to what you said about the type, and I would like you to answer that too so maybe give me a response to that, what you mean by type that you don't have the authority but also this example. I am using as an example that there are three types of fast-acting Fentanyls, I guess is the way, or rapid-onset opioids, on the market right now, and I think it is an example where REMS would be critically important because these are extremely powerful pain relievers or opioids intended to treat breakthrough pain in adult opioid-tolerant cancer patients but a dose in a non-tolerant patient could be deadly. So it is my understanding that one of these products has a REMS with very different elements from the REMS that is required of the other two. For example, the REMS dictates that only especially trained, tested and registered health care professionals can actually prescribe the product and distribution and dispensing must be done through a specially trained and registered distributor and/or pharmacist. So explain why there would be differences between the elements of REMS for these three fast-acting Fentanyls, and does that relate back to what you said before about how you can only require the REMS but not different types?

Dr. SHARFSTEIN. It does relate back to that, and I don't think all of them have what we would call formal REMS. Some of them are sort of in the intermediate stage because they had a risk management program in place when the Act was passed. But I think for the purpose of your question, it definitely relates to what I was saying. The way the law works is, it says that we need to take steps to assure safe use, and the company comes to FDA with a proposal on how to accomplish that, and there may be more than one path to get to that goal. One company might say, you know, the path that we want to take is to really work through a series of just a couple pharmacies or a central pharmacy. Another might want to put particular restrictions on which physicians so that we have the responsibility of making sure that they work. We are not going to approve something that we don't think is going to hit the mark. But they won't necessarily all look exactly the same.

In the case of the Fentanyl products, there is one that is for a film that does restrict the pharmacies, and there is another that is more of a lollipop that you put in the mouth and that one has an older risk management plan that we haven't announced the form REMS for.

Mr. PALLONE. Well, then, does this difference in authority make sense to you or would you like to have the power to dictate the type?

Dr. SHARFSTEIN. Well, I think it is very important for us to work with companies to come up with something that works and, you know, there is no question there is a lot we learn from the inner chains of companies and what we can hear from others, but I think that it is—when you find that it is taking a long time to come to agreement and when there may be a level of consistency that we would like to see if one approach really makes sense, I think that we would be very open to discussing ways that we could be able to more effectively move to closure on REMS in a way that makes sense for public health.

Mr. PALLONE. Well, my time has run out, but I have to say, this is kind of disconcerting to me, the fact that you don't have the ability to dictate the type and therefore we end up with these big differences, but I guess we will have to take it up at another time because I want to move to my ranking member, Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman. I am going to follow up on this line of questions also on the REMS.

So I think the last question was, the time it takes in negotiations. We see that across the board in the federal government, and we always say that there should be a stop clock, a backstop that eventually there is a time when you have to make a decision. You let the folks negotiate but eventually you have got to get the closure. Would a backstop provision be helpful?

Dr. SHARFSTEIN. You know, some of the REMS that we are putting into place are coming at the time of approval, and there is a lot of incentive for the company to get its drug approved, and with REMS, the standard is, we wouldn't approve the drug without it. So——

Mr. SHIMKUS. So they have an incentive to get an agreement?

Dr. SHARFSTEIN. Those are happening, but it is when the drug is already marketed——

Mr. SHIMKUS. Well, let me go to the generic/brand name. You did allude in your opening testimony that there is a difference between your ability to effect, I thought I heard, negotiations between a generic and a brand name. Can you clarify that a little better?

Dr. SHARFSTEIN. Sure. That relates to this provision about communication plans, so one of the things that we can do is require a company to make certain communications to health care professionals.

Mr. SHIMKUS. Why can't that be placed on the generic producer of the drug?

Dr. SHARFSTEIN. Someone is going to tap me on the shoulder if I get this wrong, but I think that the law doesn't allow us to do that for generics.

Mr. SHIMKUS. So the issue would be a responsibility for us to address if we are going to move forward to help assist that. OK. Thanks.

The other question I wanted to talk about was also alluded to in my opening statement, and in the FDA Week Inside Washington on January 22nd, on the second page it says, "As FDA struggles with whether to relax conflict-of-interest policies that have made it difficult to fill slots in the pharmaceutical advisor panels," so you all, the FDA, is saying we have problems filling these slots. We have a tendency, the unforeseen consequences of legislation, and I think what we are seeing to some extent is these advisory panels because of which we can't fill. We pulled up from the Web site gastrointestinal drug advisory committee where there is five openings that you all identified. Our office has personal experience with someone who had a catastrophic death because of this. What do you tell us and is there anything we need to do ease legislatively? I mean, the response was to make sure there was no conflict of interest and people weren't benefiting from their advisory role while benefiting financially but we have got to be careful that we don't go overboard and that we lose all this expertise. You alluded to

some of that in your opening statement. What can you tell us and what advice can you give us?

Dr. SHARFSTEIN. Sure. Well, this is an issue which clearly requires a balance and it is a balance that Congress faced in writing the law, it is a balance that the agency faces. On one hand, we clearly would prefer advisors who don't have conflicts of interest and it is really important for us to look for qualified advisors who don't have a conflict of interest. On the other hand, the agency needs to get the best advice in order to make the best decisions, and there are certain situations where the people who have the best advice and unique expertise are going to have conflicts of interest. We have got to somehow, you know, balance those two things, and I think the bill did a very good job and gives the agency some leeway to figure out how to do that, and within the scope of what the legislation has done, it gives us the ability to figure out the right spot, and I will be more specific. The legislation sets a cap on the number of waivers that we can have for advisory committees, and that cap goes down over time. I think it is somewhere in the ballpark of 13 percent. But we are right now well under that. I think we are granting waivers, like 4 to 5 percent of the people who are on the advisory committees are getting waivers. So without changing the law, we have the ability if we think that it is important to get certain members to grant more waivers. If—

Mr. SHIMKUS. Well, let me ask a question because my time is running. On this from the FDA Web site, you have quite a few vacancies listed there. Now, I don't know what to relate that to you because I didn't pull up the previous month or I didn't look at last year's. Is this excessive vacancies? I mean, we have got anywhere from 21 in one of the areas. Well, in fact, pharmaceutical science, there are 21 vacancies. Advisory committee reproductive health drugs, there are eight vacancies. There are nine in drug safety and risk management. That looks like there is a lot of vacancies, and if that is, then maybe we need to—

Dr. SHARFSTEIN. Right. Well, I don't like vacancies on the advisory committees. We definitely want to fill them. I actually asked the advisory committee dean whether they felt that there were more now, and they said that they have always had vacancies. They couldn't say that there are more now. Having said that, I think it is important for us to strike the right balance, and it is not a question for the statute because the statute gives us more room. If we feel the right decision is to grant people more waivers, we have got plenty of room under the statutory cap. It is really up to what the people at FDA want to do. I think the way Dr. Hamburg and I are looking at this is, there are situations where it is important for us to get the best advice from someone who requires a waiver. We need to take into account the type of conflict they may have, the type of decision that is being asked for and make a decision, but we understand that that will be necessary.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Thank you, Doctor.

Mr. PALLONE. Thank you.

Chairman Dingell.

Mr. DINGELL. Thank you.

Dr. Sharfstein, I want you to understand these are friendly questions. I want yes or no answers. You are familiar with the heparin crisis which caused 81 American deaths. Does FDA currently have the adequate resources, personnel authorities to prevent another heparin crisis?

Dr. SHARFSTEIN. No.

Mr. DINGELL. Do you have the ability to control the safety of imported pharmaceuticals?

Dr. SHARFSTEIN. Not to the extent we would like.

Mr. DINGELL. Do you have the authority and resources to address the safety of components now being imported into this country?

Dr. SHARFSTEIN. No, not to the extent we would like.

Mr. DINGELL. Do you have the authorities and resources to see to it that good manufacturing practices are properly observed overseas?

Dr. SHARFSTEIN. No, not to the extent we would like.

Mr. DINGELL. Would you please submit to the committee the number of people that you have at the different ports to assure the safety and the inspection of pharmaceuticals coming into this country, and also would you give us the number of people that you need to see to it that this is done? Please submit that for the record.

Dr. SHARFSTEIN. Sure.

Mr. DINGELL. Do you have adequate authority to keep out unsafe drug shipments at the border?

Dr. SHARFSTEIN. No.

Mr. DINGELL. Do you have authority to require manufacturers to assure the safety of their supply chain?

Dr. SHARFSTEIN. No.

Mr. DINGELL. Do you have the authority to see to it that good manufacturing practices are observed in this country in both food and drugs and abroad, yes or no?

Dr. SHARFSTEIN. Not to the extent we would like, no.

Mr. DINGELL. Does FDA have the authority to require mandatory drug recalls?

Dr. SHARFSTEIN. No.

Mr. DINGELL. Now, do you have authorities, or rather do you have cooperative management agreements or letters of cooperation between Food and Drug, the Department of Homeland Security and other agencies that have personnel at the points of entry?

Dr. SHARFSTEIN. We do work closely with other agencies at the point of entry.

Mr. DINGELL. Do you have the—

Mr. PALLONE. Mr. Dingell, excuse me. Can you speak more into the mic because I can barely hear you.

Dr. SHARFSTEIN. I am sorry about that.

Mr. PALLONE. That is all right.

Mr. DINGELL. Do you have adequate authority to require mandatory drug recall?

Dr. SHARFSTEIN. No.

Mr. DINGELL. Do you need that authority?

Dr. SHARFSTEIN. We would like that authority, yes.

Mr. DINGELL. Would you like it, or do you need it?

Dr. SHARFSTEIN. I would say we need it.

Mr. DINGELL. You have also the legislation down there in H.R. 759 which gives you additional authorities that was introduced by Mr. Pallone, Mr. Stupak, Ms. Sutton, Ms. DeGette and I. That would give you significant authorities to address your current lack of capability. Is that right?

Dr. SHARFSTEIN. That legislation has some very important elements, yes.

Mr. DINGELL. It would also give you the resources which you need of a financial character by enabling you to collect fees from both manufacturers of food and from pharmaceuticals. Is that right?

Dr. SHARFSTEIN. It does have that provision, yes.

Mr. DINGELL. And you can do that both at home and abroad. Is that right?

Dr. SHARFSTEIN. I believe so, yes.

Mr. DINGELL. And are those resources and those fees included in your budget submissions to the Congress that the Administration has submitted?

Dr. SHARFSTEIN. I don't believe so.

Mr. DINGELL. You don't? I understood they were.

Dr. SHARFSTEIN. I am sorry. For food, it is, yes.

Mr. DINGELL. For food?

Dr. SHARFSTEIN. Yes, for food.

Mr. DINGELL. How about pharmaceuticals?

Dr. SHARFSTEIN. I don't believe so, no.

Mr. DINGELL. But that is built into your budget with regard to food?

Dr. SHARFSTEIN. Correct.

Mr. DINGELL. Now, it is a curious situation that I have observed that you were in the awkward place at Food and Drug of having somebody being able to bring unsafe foods into the United States and you can't catch them at the point of entry. But you also have the problem if you do catch them, you don't have authority to seize, impound or to destroy. Is that right?

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. So you send them back out. That is right?

Dr. SHARFSTEIN. I believe so. Often that is what happens.

Mr. DINGELL. And they then bring them back in. Is that right? Through another port of entry.

Dr. SHARFSTEIN. I think they can try, yes.

Mr. DINGELL. Do you have that same problem with regard to pharmaceuticals?

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. So that problem exists in both places. Now, you have problems with unsafe commodities being brought in, foods and pharmaceuticals, and you also have some that are overaged, improperly stored, contaminated, filthy, improperly packaged, counterfeit, and you also have some that are full of inert substances. You mentioned talcum powder and things like that coming in. Do you have authority to deal with those?

Dr. SHARFSTEIN. We have some authorities but not enough.

Mr. DINGELL. Do you have enough?

Dr. SHARFSTEIN. We don't have enough.

Mr. DINGELL. As proven by heparin.

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. And of course, you have coming into this country from China on a fairly regular basis, from Mexico and other places, unsafe foods and pharmaceuticals and I can recall mushrooms, I can recall berries, I can recall tomatoes and jalapeno peppers. I can recall the heparin scare and a large number of others. This an ongoing and continuing problem, is it not?

Dr. SHARFSTEIN. Absolutely.

Mr. DINGELL. And you lack the Congressional support in both authority and money to do the job that you need to do to protect the American people. Isn't that right?

Dr. SHARFSTEIN. Well, we very much want to do more.

Mr. DINGELL. I don't want you to be afraid to say that we haven't given you the authority you need—

Dr. SHARFSTEIN. We want more authority.

Mr. DINGELL [continuing]. If it is the truth because we are going to try and get it for you.

Mr. Chairman, I thank you for your courtesy.

Mr. PALLONE. Thank you, Mr. Dingell.

The gentleman from Pennsylvania, Mr. Pitts.

Mr. PITTS. Thank you, Mr. Chairman. Going back to this concern for counterfeit drugs, there is a growing global threat from counterfeit medicines. For example, in 2008, counterfeit medicine article seizures rose 118 percent in the European Union, and 8.9 million counterfeit medicine articles were seized by E.U. customs officials. Over just a 2-month period in 2008, the European Commission seized 34 million counterfeit pills including antibiotics, cancer, cholesterol and antimalaria medicines. Does this staggering increase in counterfeiting in places like the E.U. present concerns to the United States, and can you quantify it for us?

Dr. SHARFSTEIN. It definitely does present concerns, and I think, you know, the problems with counterfeit products, first of all, they can be dangerous in and of themselves, but second of all, they can fail to treat the condition that the patient has and the patient can get much sicker if they are taking medicines that are ineffective or subpotent. So it presents a serious problem and I think the problems that we see globally are very much a potential threat to the United States.

In terms of quantifying, I can't unfortunately quantify how many counterfeits are in the United States. We do that reports that we have been investigating have gone up over the last 2 years so that our investigators at FDA are hearing about this problem more, but we do think that in general we do not have a huge problem with counterfeit in part because we have a closed—a generally closed system. When pharmacies order medications, they can get them through licensed wholesalers, they can get them from licensed manufacturers, but we know that there are ways for other products to enter the legitimate supply chain and that makes us concerned. You may remember in 2003 there were several million, I think, pills of Lipitor that were counterfeit that got into pharmacies, and there are other problems too. Recently we had a situation where a truck full of insulin was stolen and then the insulin started showing up later, and we didn't know whether the insulin had been adequately refrigerated and it had sort of reentered the supply

chain in a way that could potentially have been quite dangerous to patients. So there is no question that the problems seen around the world are of concern to us and we think that we do need additional work here to really secure the supply chain in the United States against this potential threat.

Mr. PITTS. When the U.S. authorities interdict counterfeit drugs here in the United States, what occurs? What is done with those drugs?

Dr. SHARFSTEIN. When we actually find the drugs and we know that they are counterfeit? I am not sure, but I think they are destroyed. If we identify products that are, you know, in the supply chain that are counterfeit, I can double check, but I think they get destroyed.

Mr. PITTS. Where are the major gaps, in your opinion, as far as interdiction of counterfeit drugs here in the United States?

Dr. SHARFSTEIN. The major gap is that we don't require a pedigree for the product to go all the way from the manufacturer to the final sale. If people are ordering from the right places, they can get medicines that are safe and not counterfeit. There are opportunities for counterfeit products to potentially get in without a clear requirement where we are holding each person in the chain responsible for making sure that they only have legitimate products. So the kind of provisions that we would like to see are that each person in the supply chain as it goes from the manufacturer to the wholesaler, they are responsible. If they let something in that is not legitimate, then there is a real penalty for that and every single person in the supply chain, every single company is responsible for making sure those products are legitimate, and that would require a new authority.

Mr. PITTS. Do you have a regular system or procedure for testing drugs that are coming in the United States that you pursue?

Dr. SHARFSTEIN. We do do some tests. We do some targeted sampling based on where we think the risk is but it is really only a small part of the solution, the testing. There is no way we could test our way out of the problem just because of the sheer volume of imports.

Mr. PITTS. What is the greatest need that you have as an agency as far as addressing this problem?

Dr. SHARFSTEIN. I think the greatest need is the ability to enforce the supply chain requirements across the supply chain. You know, we have been working on and are about to come out with a process for unique numbers for each kind of bottle of pills but we don't have the authority to say you are responsible for making sure that every person when they get the medication that it is legitimate medication. That is what we would like.

Mr. PITTS. Thank you, Mr. Chairman.

Mr. SHIMKUS. Would the gentleman yield for one second?

Mr. PITTS. I will yield.

Mr. SHIMKUS. But that discussion was all about the legal distribution chain. You haven't even addressed the illegal Web sites and the illegal mail order sites that if some senior goes on a Web site, clicks on 90-day supply of Lipitor and it gets mailed to them, there is no way. We don't know. Is that correct? I mean, that was

a good discussion about legal process, of all the good actors. I think the concern that most of us have is the bad actors.

Dr. SHARFSTEIN. We have brought some cases recently against bad actors and legitimate chain and the ability of products to infiltrate the legitimate supply chain is something that we need to be very vigilant about, but you are right. You are raising a separate issue that is very important and I think this gets a little bit to the issue that Congressman Buyer and Congressman Matheson were raising about destruction authority and other things, and that is also an issue that we care about.

Mr. SHIMKUS. Yes, and I only bring it up because there is really—I agree with your statements but I think for both of us it is that other issue that has us more concerned than anything.

I appreciate the gentleman yielding.

Mr. PITTS. Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you.

The gentlewoman from the Virgin Islands, Mrs. Christensen.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman, and thank you for holding this hearing, and welcome back, Dr. Sharfstein.

First of all, I can attest to the fact to the answer to Chairman Dingell's question about collaboration with other agencies because Customs and Border Protection acts on behalf of FDA at the Puerto Rico transit station—and your staff knows where I am going, I can see them nodding—to confiscate medication going to and from the Virgin Islands, but I am not sure if you are aware of this problem but I have to bring it up, and your staff is aware of it. We are outside of the U.S. customs zone. We are fully part of the United States. We are outside of the U.S. customs zone. All of our pharmacists are U.S. trained, and while they are locally licensed, they have their U.S. DEA license and are governed like the Virgin Islands are in general by all the U.S. laws and they are governed by all FDA rules and regulations. They order their medication including my hospital pharmacies, which are also overseen by JCAHO and CMS. They order their medication from distributors in the States. These are either U.S.-made medication or something that FDA has approved for importation into the United States. They cannot send it back to their distributor. They are prohibited because we are outside of the customs zone from sending it back to their distributor if they are oversupplied, if they are damaged, if they are expired. It is an extreme burden on my pharmacies. My hospital pharmacies were cited by one of the certifying agencies for having too many expired drugs in the pharmacy.

If we could craft some narrow language, and we have tried, that would just allow our pharmacies to send their medication back to the place that they brought it from, would you be willing to take a look at that?

Dr. SHARFSTEIN. Absolutely, and I do recall your raising this issue before and I know that there are people at FDA who have been actually in touch with entities in the Virgin Islands to work on this.

Mrs. CHRISTENSEN. Yes, we have had some conference calls.

Dr. SHARFSTEIN. So I am extremely sympathetic to the situation that they were in and I think we would like to find a solution.

Mrs. CHRISTENSEN. I appreciate that. And the other question is about importation. Well, I don't consider ours importation or reimportation of drugs because they are U.S.-made drugs, U.S. pharmacies, it is U.S. jurisdiction. But Congress and FDA acknowledge that there have been numerous safety issues related to drug importation, and I voted against it when I had the opportunity. One of the issues I am concerned about from a safety perspective is the importation of products subject to the REMS requirements that have been discussed in other ways here today. Does the FDA support this posture that they can be reimported subject to the REMS requirements, and how does FDA view the reimportation safety concerns as they relate to the REMS process? And would FDA ever under any circumstances consider an exemption of certain drugs under reimportation policy if it would lead to the obfuscation of the REMS requirements? Is that clear?

Dr. SHARFSTEIN. I think I understand. You know, the Administration supports finding a safe and effective way for patients to obtain medications from other countries but it is a challenge because there are a lot of safety concerns, and certainly one of the safety concerns that would have to be overcome is trying to figure out what to do with the products that have a narrow therapeutic window. Another way of saying that, where you are worried that they could actually do more harm than good where you have a REMS in place or other medicines where it depends on how they are used, and that very much would be an issue for us, I think, and we would not want people to get medications without the kind of controls that are needed to ensure their safe use.

Mrs. CHRISTENSEN. Is there something that we need to do to, or is there something the improvements that need to be made or becoming more assured of the safety and use of the REMS process? Is there something that we need to do? Is there something that FDA can do administratively?

Dr. SHARFSTEIN. I don't think there is an issue before Congress on this point right now, but if there is, we can be in touch. But I think the premise of your question that there are certain drugs we have to be very careful about, that does underlie FDAAA and that is something that FDA feels very strongly about.

Mrs. CHRISTENSEN. Thank you.

Thank you, Mr. Chairman.

Mr. PALLONE. Mr. Burgess.

Dr. BURGESS. Thank you, Mr. Chairman, and again, Dr. Sharfstein, thank you for being with us and staying with us late this afternoon.

On the issue of resources, we have heard I don't know how many times in this committee and the Subcommittee on Oversight and Investigations about inadequate resourcing of the agency and that the resources haven't kept pace with the increase in demands placed on the FDA, the fact that now you are having to really function as almost a global agency with budgets that 10 years ago seemed adequate but now you seem significantly underfunded. It always happens. In fact, I was on this committee for several years before I realized that the funding actually comes from the USDA appropriations bill, not through HHS. That funding structure some-

thing that you all have to deal with but should we consider some way modernizing how Congress funds the FDA?

Dr. SHARFSTEIN. You know, I think over the last few years FDA has gotten a tremendous amount of new resources and the subcommittees, both of which I testified at last year, were extremely supportive of the agency, and the agency really has been using those resources to develop a real foundation for the future on these issues. I think that it is not just resources that are an issue when it comes to an issue like safe drugs and imported safe drugs. We need to be able to secure the supply chain, hold people in the supply chain accountable, set good standards—

Dr. BURGESS. I don't mean to interrupt you, but I will run out of time here.

Mr. Chairman, if you will just make note that the witness testified that they have all the money they need and Congress does not need to supply any more.

But it begs the next question, and I know it is a drug safety hearing, but you must get a tremendous volume of new drug applications. Is that correct?

Dr. SHARFSTEIN. I think that there is a tremendous amount of work when it comes to the new drug applications and additional indications for existing drugs, so there are a lot of different types of applications that the agency has to handle, yes.

Dr. BURGESS. Do you have any idea as to the magnitude of the backlog?

Dr. SHARFSTEIN. Well, there is not really a backlog when it comes to the new drug applications. We are on a clock and we do our best to hit the goals of reviewed timetables. When it comes to generic drugs, there is a backlog. It is a different type of review process, a different type of application, and there are several thousand applications that are kind of in the queue to be approved.

Dr. BURGESS. Well, for example, we got funding for the National Institute of Health in the stimulus bill, a significant amount of money, and the idea was, of course, to generate new research and new discoveries. Do you have what you need to keep pace with the rapidity of those new discoveries and new developments?

Dr. SHARFSTEIN. That is an excellent question, and slightly different than just reviewing the applications. I think that FDA, and Dr. Hamburg has been very engaged on this issue. We feel that the agency needs to do a lot more to be able to review the products of the 21st century, and that involves updating and upgrading our scientific standards for review and it involves a lot of needed investments, not just by the government but by academia and others, in what we call regulatory science, which is the science of how you know whether something is safe and effective. For example, we want to be able to identify a safety problem very quickly in the lab and not have a company spend all this time and money in development and then find the safety problem; let us identify that quickly. If there is a way on the effectiveness side to find a marker that a drug will be effective without having to require a tremendous and long amount of time before we show that it works, that is just an enormous benefit to the drug development process, and that is separate from the review of any one application but that area of regulatory science and those kinds of investments are extremely impor-

tant. The President's budget for the first time has an initiative on that but over the course of the future this is where we think that there needs to be a lot more done.

Dr. BURGESS. Well, just as a case in point, a real-world example, yesterday the Alzheimer's association was on the Hill visiting every office asking for a significant plus-up in funding for Alzheimer's research, a noble goal, a worthwhile goal. This comes on top of the reauthorization we did at NIH back in 2006, level funding of \$30 billion a year to increase 5 percent a year. I don't know that we have ever met those goals. But then the \$10 billion in addition to the authorized amount that we gave in the stimulus bill, now we are asking at least in the Alzheimer's legislation that Mr. Markey has, another \$2 billion to put forward to the research for new Alzheimer's drugs. Can you guys keep up with that if you have that kind of push in the pipeline for new products coming down?

Dr. SHARFSTEIN. I will tell you the analogy that Dr. Hamburg uses when she talks about is of a rower with one very muscular arm and one kind of scrawny arm, and if we are pouring a lot into basic medical research but we don't have the science to decide whether the products are safe and effective, then you don't get a system that moves forward. It kind of goes in circles. You don't see the treatment——

Dr. BURGESS. And are you aligning yourself to that, to making a more muscular——

Dr. SHARFSTEIN. Yes. And in fact, a few weeks ago, Secretary of Health Kathleen Sebelius went out to NIH with Dr. Collins and Dr. Hamburg and we announced a whole set of collaborations with NIH to bridge the gap so that it is not that money goes to NIH and then here is FDA on the other side but that we are going to have in addition to a public meeting and open docket for suggestions on how we can work together, we can have a council that is going to meet and oversee a whole new range of collaborations, and for the first time both agencies are putting in money to fund this kind of research in academia around regulatory science.

Dr. BURGESS. But at the present time, to the extent that those new discoveries are arriving on your doorstep, there is no backlog? Those applications are receiving timely review and——

Dr. SHARFSTEIN. It is not a question of the timeliness of the review, it is the tools we have. We would like to upgrade the tools we have for the new types of products.

Dr. BURGESS. Are all those applications online? Is that all in an electronic database?

Dr. SHARFSTEIN. We are moving towards full electronic submission but the problem is——

Dr. BURGESS. So the applications are paper applications?

Dr. SHARFSTEIN. In some cases, but I think we are moving pretty quickly to electronic, but I think the issue is——

Dr. BURGESS. But, you know, here, and I will just give you a real-world example. If this were a class-action lawsuit, for example, a big law firm, any of the big law firms downtown or in downtown Dallas would hire the people to digitize that data and then have it done within a couple of months' time in order to make their case either pro or con in the legal action. This is something that is done

all the time but outside organizations. The FDA should be the leader on this.

Dr. SHARFSTEIN. There is no question that we need to have electronic data submissions, and we want to do it in a way that the data comes in so that it can be analyzed very efficiently. The challenge is, it is not so much the review of the application that comes in, it is that we don't get the applications, products don't make it all the way to the point where they have enough evidence to get to FDA's doorstep. That is the kind of gulf we are trying to cross by working with the NIH, that they do the research, they go, oh, maybe this product works. Then how do you get it from there to the point where you can do clinical trials? I mean, how do you—what is the right kind of clinical trial to do, what is the right tool to know, how do you get the companies in, ready to invest.

Dr. BURGESS. And after companies have made that investment and they come to you for the approval, that is the part of the chain that I am worried about, that you have the tools you need to be able to get these things to the people who so desperately need them.

Dr. SHARFSTEIN. I agree with that completely, and we also want more drugs to come to our doorstep than are coming now, more applications. We would like to see that happen because there are a lot of people who have diseases that need medicine.

Dr. BURGESS. I don't know what time frame would be the correct unit, but how many new drug applications per month or quarter or fiscal year?

Dr. SHARFSTEIN. I think it is a ballpark of about 25 new, completely new drugs getting approved by the FDA roughly every year.

Dr. BURGESS. How many applications, though, how many new drug applications that seek approval will you get a year? So 25 make it through the—

Dr. SHARFSTEIN. This is Dr. Woodcock from FDA. About 30 to 35. You know, that is my point about we would like to see more. But to do that, we have to help the discoveries bridge the way to the point of FDA application.

Dr. BURGESS. Interestingly, Dr. Zerhouni at NIH 8 years ago told me that they were working on, I think it was no fewer than 88 drugs to deal with obesity. With that kind of pressure in the research pipeline, you guys are going to have to be really precise and efficient to be able to handle that kind of research coming in your direction.

Dr. SHARFSTEIN. I think that is true. What we want to do is help NIH as it is investing in those 88 or however many it is products, pursue that investment so it is pushing the products closer to an FDA application rather than, you know, being all these different steps to get there. And so that is one of the things we are going to work with them on. If NIH is going to pay for a trial, what is the right way to design that so that we get really good usable data for an application. So it is not so much once the application comes in, we need better tools to review them, but it is how you get more applications of promising therapies. That is what Dr. Hamburg is extremely committed to and why we are doing this big product with NIH.

Mr. PALLONE. Dr. Burgess, we are actually going to have a second round, so I just want you to know.

Mr. Braley.

Mr. BRALEY. Thank you.

Dr. Sharfstein, I want to start with a word that we hear still today frequently called mail order drugs, and in this Internet age, isn't that somewhat of an oxymoron? There is a very specific reason I am asking you this question. We heard our colleague Dr. Gingrey spend his time that he had in his opening instead of talking about drug safety blasting the health care legislation we are considering right now. But when you have 47 million Americans without access to health insurance and a lot of people losing their jobs with employer-based health care coverage and you have got people who are in prescription drugs who suddenly have no means because they can't afford to pay their COBRA payments without a job who go online like many of us and surf for some answer to their medication needs. There are endless Web sites out there of predatory companies looking to see what may or may not be an actual pharmaceutical to somebody desperate for treatment. Would you agree with that?

Dr. SHARFSTEIN. I think it is a recipe for tragedy.

Mr. BRALEY. And we all know that the problem is, your agency has limited resources you are dealing with. Research applications, you are dealing with enforcement issues overseas, you are dealing with enforcement and compliance in domestic manufacturers. So I guess my question is, if we do nothing to improve access and affordability for prescription drugs, aren't we just inviting chaos as consumers look to these disreputable online companies, and I am not lumping all online companies into that category but there are plenty of them out there. Aren't desperate people going to resort to desperate measures to try to solve their health care needs?

Dr. SHARFSTEIN. I think there is no question that health care reform that gets more Americans access to prescription drug coverage is extraordinarily important for avoiding the kinds of problems we are talking about.

Mr. BRALEY. Thank you. One of the things that I wanted to talk to you about was your remarks about the Sentinel Initiative because I am interested in learning more about that, what it was based upon, what model it was based upon and how it is going to achieve the objective of a national integrated electronic system for monitoring medical product safety. And Dr. Christensen mentioned JCAHO, which is looked to by many people as a forerunner in setting up a Sentinel Event Reporting System with root cause analysis and an integrated approach to trying to get to the bottom of patient safety issues. In its first 10 years of existence, the Sentinel Event Reporting System averaged annually 300 reports, which is an abysmal statistic given the high number of medical errors that occur in this country every year. So tell me how this Sentinel Initiative that FDA is pursuing is going to achieve the objective and the access data goals that you have identified and truly reach a comprehensive reporting system that is going to get to the heart of patient and drug safety?

Dr. SHARFSTEIN. Sure. I appreciate the question. What we are doing and the sentinel system at JCAHO are very, very different.

They have the same word but they are very, very different. They are, I think what you are describing is sort of a reporting system where people actually have to report. That is not what the FDA's sentinel system is based on. The concept is that there are data resources out there, generally large, integrated health systems, where you have data for millions of Americans who are taking medications and that we can use that information in a way that is completely protective of their confidentiality. In fact, the data we are looking at doesn't come to the federal government, it is done by the systems themselves. They look into their system to answer key questions about drug safety and over time we put into place a system to look in advance. In other words, if we have a concern that a particular product might cause a problem, we can program it so that if we see that when patients are getting it, it automatically lets us know. That is the long-term goal. So——

Mr. BRALEY. Let me just interrupt you briefly to add another component to this, because my time is running out. There has been a big push not only in the American Recovery and Reinvestment Act that we passed earlier in 2009 but also in this health care bill that we have been talking about to move aggressively toward electronic medical records, which we all know is one way to try to deal with drug interactions and to dramatically reduce the number of drug errors. So is that another reason why getting it right on EMR is so important in addressing some of the goals of this Sentinel Initiative?

Dr. SHARFSTEIN. Absolutely. If we have more patients with effective medical records and we are working with the Office of the National Coordinator to make sure the standards on those records are good for this kind of work, then we will be able to tap into more Americans' experiences with medications to identify whether there are legitimate safety issues that we have to respond to. So where we are now if that we are working with certain health care systems that have data and we are setting up basic standards so that they will be able to respond to inquiries. It is a system where we don't need anyone to volunteer anything. Once we have a question, they go out and they just program their data set and they tell us whether they are seeing that, and it is a network so it is not just one big database. It is, you know, we are going to go up to New England and there is a data set there, there is a data set in California, and we are going to be able to look in a much quicker way than we can do to see if there are safety signals emerging. And there has been a lot of work done at FDA. We are constantly reviewing how this is going to make sure we are keeping it on track. It is a very ambitious project but there has been a tremendous amount of leadership at the agency on it and we are very appreciative of the support we have gotten.

Mr. BRALEY. Thank you. I will yield back, and I would just encourage you to keep us informed on the progress you are making in the rollout of that system.

Dr. SHARFSTEIN. Sure.

Mr. PALLONE. Thank you.

The gentleman from Kentucky, Mr. Whitfield.

Mr. WHITFIELD. Thank you very much.

I have a relatively simple question. As you continue to work and develop the REMS program, and I had mentioned in my opening statement about NASPER, the national prescription drug monitoring system. I was curious, have you yourself worked or your agency worked very much with the DEA or SAMHSA in implementing this national prescription drug monitoring system?

Dr. SHARFSTEIN. It is an excellent question, and that system is primarily dedicated to the schedule drugs, and we have been having some public meetings about how to ensure the safe use of certain schedule drugs that have very important medical uses. They are long-acting opiate medicines. You know, our reach in the REMS program goes really to the manufacturers and what they can do, but we are very aware that there are other key players and we have been in discussions with DEA and others to try to figure out what the right balance is. We clearly know that patients benefit from pain relief and it is extremely important. On the other hand, we don't like to see the fact that patients can die of unnecessary overdoses or there can be diversion. So it is a combination, and we have some tools to put on the table to help with this balance and we are very aware that the other agencies do and the prescription drug monitoring program is very much part of the discussion.

Mr. WHITFIELD. Well, I appreciate that, and of course, REMS is designed to minimize risk for patients and certainly that is the same goal of NASPER as well to give the health care providers more information. So I hope that you all will keep that in your minds as we move forward on trying to obtain adequate funding to fully implement NASPER.

Dr. SHARFSTEIN. Thank you. That is an excellent point.

Mr. PALLONE. Dr. Sharfstein, you describe in your testimony the importance of moving from a reactive approach to drug safety problems to one that prevents such problems from occurring in the first place. Obviously prevention is what we are all about in every aspect of health care. As you know, the committee worked very closely with the FDA to develop and pass the Food Safety Enhancement Act this past summer. We are now waiting and waiting for the Senate to pass its version, which we hope will be very similar to our bill. I understand they did pass a bill out of committee. In my view, one of the most critical components of the food safety legislation was giving the food industry more responsibility to ensure the safety of their foods and giving FDA more authority to ensure the preventive safety controls are in place, and you mentioned this provision in your testimony and stated that FDA is taking steps to begin making this kind of shift within your current authorities. And what I am trying to understand is whether your current authorities are adequate to accomplish this.

The Food and Drug Administration Globalization Act of 2009, that is the bill that was developed by Mr. Dingell, myself, Mr. Stupak and others, and that contains a similar provision to that in the food safety bill. Specifically, section 204 of that bill would require drug companies to develop and implement a quality risk management plan to incorporate risk identification and control into the production processes. The plan would, for example, require the company to assess the competence of potential suppliers of raw materials or ingredients. It would also require the company to conduct

periodic onsite audits and carefully monitor the safety of drug ingredients, and this plan would be available for FDA review during inspections. So what I am trying to find out is whether you think this approach is workable and necessary for drugs as we did for foods, and would it help FDA's efforts to shift to a more preventative-based drug safety system if the agency had that kind of enforceable authority?

Dr. SHARFSTEIN. Thank you. It is a great question, and it is in fact true that the same principle that underlies the food safety bill and a lot of the authorities that is needed in the medical product arena also. We do think that new authorities are going to be necessary for FDA to have confidence in the preventive-oriented approach. Right now, FDA inspectors are at the border under a legal standard that we can hold something if there is an appearance of adulteration, but we can't require, we don't have access, because we can't require people to have current registration for, you know, just those facilities that they are making. We can't require them to present information about their products meeting key safety standards like having a preventive plan in place. And so we are not operating under a paradigm that is really focused on prevention, and we would like to make that shift and there are definitely elements in the bill that would accomplish that.

Mr. PALLONE. I appreciate that. When we did this Globalization Act, we had the four areas you mentioned, medical devices, there is also cosmetics, and of course ultimately we would like to develop legislation or pass legislation for all four, but we separated out the food safety because we were making more progress and we felt that that was the most likely that we could move. But now we want to move to certainly deal with the drugs and ultimately with the others as well. So I just ask that you—you know, I know that you provided a lot of help to us as we developed the food safety legislation. We would like to have the same cooperation and help as we move towards drug safety and the others.

Dr. SHARFSTEIN. Well, we really appreciate the subcommittee's leadership in this area.

Mr. PALLONE. Thank you.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman.

This is a good line of questions and debate and instruction, so I am glad we are going down this route. I want to go back. We were involved with the legislation that is pending over on the Senate side now and so it is a template for where we want to move but we need to get some clarification. Does the FDA have tools at its disposal to have a company take its drug off the market? Do you have the tools right now?

Dr. SHARFSTEIN. There are mechanisms for FDA to have drugs—you mean if a drug is unsafe?

Mr. SHIMKUS. Right.

Dr. SHARFSTEIN. Yes, there is a process for that.

Mr. SHIMKUS. So we do have the tools?

Dr. SHARFSTEIN. If there a safety problem with the medicine so it is no longer safe and effective, yes, there is a process for that.

Mr. SHIMKUS. And so in the past years you have asked drug companies to take drugs that are identified as being bad off the market, have you not?

Dr. SHARFSTEIN. Yes.

Mr. SHIMKUS. Has any company ever refused to do so?

Dr. SHARFSTEIN. I have to go back, but not that I know of.

Mr. SHIMKUS. There has been——

Dr. SHARFSTEIN. I shouldn't say not that I know of. I think we would have to get back to you because there may be some examples of that. But I think that you have to distinguish between—there are two things. One is the products and the other is the manufacturing, whether there are manufacturing issues that could come up as well.

Mr. SHIMKUS. A follow-on question, because we really want to drill down because we know you have got the ability to do—we just don't want you to say boom, here is all this new stuff if there are things that are doing successfully now. We don't want to create multiple additional new levels of bureaucracy, we want to build on what is working now. And so that is why we want to be very specific with our questions.

Dr. SHARFSTEIN. Sure. The one thing I would say is that it is important that, you know, there may a process to accomplish something but if that process is so burdensome and time consuming, it may not be fully protective of public health. So as we get back on these things to provide technical assistance, it may be that, yes, there is a process but we would like a better process, a simpler process that can be more effective.

Mr. SHIMKUS. In your response to Chairman Dingell, you stated that you needed additional authority to require manufacturers to implement quality risk management plans. And the follow-up question is, do you actually need this authority or is that something you can do now? Could you just incorporate this into your good manufacturing practice regulations?

Dr. SHARFSTEIN. We feel like we would need the authority.

Mr. SHIMKUS. I think we need to talk more.

Dr. SHARFSTEIN. I am always happy to talk more, but I think that we——

Mr. SHIMKUS. That is the whole thing. When we move legislation, we are going to get more specific. You can help educate us and we are going to be getting you all the resources you need.

Dr. SHARFSTEIN. They are very different, and it is similar to the food safety language, because even though there are food GMPs that we get authority that the food safety to set preventive standards.

Mr. SHIMKUS. But having been in the room on that, we struck a good balance, that we didn't go overboard and that we brought industry at the table so that we didn't duplicate things.

Dr. SHARFSTEIN. I agree.

Mr. SHIMKUS. And that is where we want to be very, very—because we want to be helpful. We don't want to be harmful. We don't want to create such—and we talked about this gap. You talked about really this gap from NIH to FDA, and you know what ties the companies over to continue to develop these new drugs, and that is the certainty that if they are successful, they have a patent

and they have a return on that investment. And of course, we are always attacking that patent. We do want to attack—I have always been in the position that when they game the system and extend that, but I have always supported these folks who are taking the risk all these years, that gap, the only thing that keeps them going is that assurance that there is going to be a return on that investment based upon at least some period of time where they have exclusive rights to sell that drug. Isn't that correct?

Dr. SHARFSTEIN. I think it is very important that companies have some protection.

Mr. SHIMKUS. And I am going to end on this as far as my line. I do appreciate this. As we move forward, I have great respect for the chairman of this committee. There are times that we have agreed and we worked well together and there are times when we fought and we still are friends. And so I look forward to both times as we move forward.

But I also want to be careful, and I am also on the high-tech committee here and I understand the benefits of digital records, and we are always going to fall into this concern on privacy and the collection of data, and it is a tough balance. So when we hear words about collecting data, information on personal records that help us do something, I think that is going to be easier said than done.

Dr. SHARFSTEIN. Right. And just to be clear, what I was talking about, the sentinel system, there is no personal data at all that comes to FDA. It is done by the health systems themselves, the studies.

Mr. SHIMKUS. I am just telling you, most data breaches are people stealing data and——

Dr. SHARFSTEIN. It is a very serious issue——

Mr. SHIMKUS [continuing]. Selling it with flash drives and stuff, so thank you, Mr. Chairman.

Mr. PALLONE. Thank you.

The gentleman from Texas, Mr. Burgess.

Dr. BURGESS. Thank you, Mr. Chairman. This is a good hearing and a good discussion. I hope we actually have an opportunity to have a similar discussion regarding medical devices at some point in the future because they deserve no less of our scrutiny.

Dr. Sharfstein, I wasn't in the room when Mr. Dingell was asking questions, but some of them have been sort of reintroduced now by Mr. Shimkus. On the border authority—we all remember the story of the tomatoes a couple years ago and the unfortunate discovery at 5:00 on a Friday afternoon that it was Mexican peppers that were causing salmonella outbreaks that had riveted the news shows for the whole summer, but the FDA lacked the authority to actually stop the importation at that point. Have you identified the authority that you need there to keep this occurrence from happening in the future? Are there things you need from us to be able to have that authority if you have identified the authority and you lack it?

Dr. SHARFSTEIN. With respect to food particularly?

Dr. BURGESS. Particularly with respect to food, but we are going to get into some of the pharmaceuticals in a minute.

Dr. SHARFSTEIN. There is no question we need more authority because we want to shift to prevention. We need to be able to see—

Dr. BURGESS. So can you identify for us specifically what that authority is that you need?

Dr. SHARFSTEIN. Well, I think that that is where we worked with the committee on the legislation that is hopefully going to pass, is going to address that gap. There are sections that relate to what is required to import food.

Dr. BURGESS. And is the language in the bill that Mr. Dingell said was languishing safely in the Senate, is that language enough? Is it going to provide you enough of the authority of what you need to have?

Dr. SHARFSTEIN. Yes, we support that legislation because it is going to be an enormous step forward for how we can assure the safety of imported food and domestic food.

Dr. BURGESS. So any changes that occur over the other body then would need to be scrutinized pretty carefully to make certain that they didn't strip away the authority that you have identified that you will need?

Dr. SHARFSTEIN. Well, there is no question. All these provisions are extremely important, and it is very important that, you know, we look at all of them as they get modified in the legislative process.

Dr. BURGESS. Another story that really just riveted the headlines 2 years ago was the Chinese heparin story. What has happened? We had a hearing I think in April or May of 2008. It hasn't really been in the news stories. What is happening in that investigation now? Is there anything new that has come up from your looking into the manufacturer of the isolation of heparin overseas? Are we still importing the active pharmaceutical ingredient from overseas? Where are we with that?

Dr. SHARFSTEIN. There is certainly a huge level of import from China for heparin. What has really happened since that time is after the source of the problem was identified, there was a new standard written for heparin that has been adopted by companies and regulators around the world. It has been incorporated into the USP, which is sort of the standard-setting body, so that now—previously it wouldn't have caught the problem, oversulfated chondroitin sulfate.

Dr. BURGESS. Right. It was a clever contaminant to hide behind.

Dr. SHARFSTEIN. Right. Much cheaper than heparin, but evaded the tests, went below the radar. FDA played a critical role in identifying how you can find that contaminant, demonstrated that when you add that contaminant to heparin you get the problem in animals, and then set up a standard that has been incorporated around the world and we haven't seen those kinds of reports that we were getting since that time.

Dr. BURGESS. Well, now, heparin wouldn't truly be regarded as a biologic but there has been some question in this committee about how your agency would administer the follow-on biologic approval process. So in light of everything, do you feel like you have an adequate ability to safely and properly monitor and implement the approval process for follow-on biologics or what are referred to as follow-on biologics?

Dr. SHARFSTEIN. From the perspective of the supply chain, I think for all, you know, medications and biologics, we would like to see strengthening of the supply chain including the things that are there now but——

Dr. BURGESS. Right. The supply chain in this instance just showed the weakness, though, of the process used to identify contaminants. In approving follow-up biologics, I mean, it underscores how important the safety aspect is. Do you feel that with what you have available to monitor and screen the follow-on biologics in that process? We have had that debate somewhat in this committee. We have never had you guys in to ask you about that. We have had the Federal Trade Commission in, which I never understood. So now that I have got you here, what about the discussion on follow-on biologics?

Dr. SHARFSTEIN. I think that the follow-on biologics sort of supply chain issues are the same as for the regular. In some cases, they are the same companies making them. So——

Dr. BURGESS. No, outside the supply chain, just the overall safety of follow-on biologics.

Dr. SHARFSTEIN. That is something that is very important to base on individual products and the best science available, and FDA believes that with adequate resources and the right——

Dr. BURGESS. You said you had all the money you needed, remember, the previous question.

Dr. SHARFSTEIN. I don't—we could check the transcript on that one. I think that what we would like is the flexibility to have standards that are based on the best available science for particular products, and with that in place, we would explain how we are setting up those standards and be able to do it in a way that could get products on the market that could be enormously important to the public.

Dr. BURGESS. So where are we in that process now? We had some language in the bill that we passed, and goodness knows what is going to happen to that bill, but are you all waiting for Congress to do something?

Dr. SHARFSTEIN. I think we are certainly waiting to see what happens with health care reform because there is some language in there, but I think that we would also look to the authority we have to decide whether it would make sense for us to move forward without new language, but that is not something we have reached final decision on.

Dr. BURGESS. Is there a product out there right now that is awaiting your ability to be able to offer those approvals or direct further study?

Dr. SHARFSTEIN. There is certainly a lot of interest in the industry but I don't know if I could point to a particular product.

Mr. PALLONE. OK.

Dr. BURGESS. Thank you, Mr. Chairman.

Mr. PALLONE. You are welcome.

Let me thank Dr. Sharfstein. Thanks a lot. This was very helpful, and we appreciate it, and obviously we would like to move forward on the drug safety issue as we did on food safety. You actually said that you are going to follow up with certain written responses in some cases, so I would appreciate those as soon as pos-

sible, and members can submit additional questions for the record as well. I am going to try to get those submitted to the clerk within the next 10 days, so I would ask members if they want to submit written questions, to give them to us within the next 10 days, and then after that we would ask you to get back to us as quickly as possible.

Dr. SHARFSTEIN. OK. Great.

Mr. PALLONE. Thank you again, and without objection, the hearing of the subcommittee is adjourned.

[Whereupon, at 4:22 p.m., the Subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Henry A. Waxman
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

APR 30 2010

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the March 10, 2010, hearing entitled "Drug Safety: An Update from the Food and Drug Administration," before the Subcommittee on Health, Committee on Energy and Commerce. This letter provides responses for the record to questions posed by certain Members of the Subcommittee at the March 10, 2010, hearing, as well as in your letter dated March 25, 2010.

As you requested, we have addressed our responses to each Member. We have restated each question below in bold type, followed by FDA's responses.

Representative Tim Murphy

- 1. Could you please get back to us and let us know how we could keep up to date on the latest scientific evidence (pertaining to vaccines) here?**

Scientifically accurate information pertaining to vaccines is available on the FDA Web site. This includes Web pages devoted to vaccines and related research, as well as annual reports and other relevant information from FDA's Center for Biologics Evaluation and Research (CBER). FDA's vaccines Web page can be found at: <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/default.htm>. Furthermore, external Web sites, such as those for the Institute of Medicine, Centers for Disease Control and Prevention, National Institutes of Health, and Johns Hopkins Bloomberg School of Public Health (Institute for Vaccine Safety), include information on vaccine use, safety, and reviews, which may provide additional information.

- 2. How are you ensuring that vaccine makers are using the latest and safest innovations in vaccine design?**

FDA has scientific and regulatory expertise, as well as our own laboratories, to adequately assess the safety, purity and potency of vaccines for use in the United States, and strives to keep this expertise up to date. Throughout the clinical development of a vaccine, we assess the available data and provide scientific advice to vaccine manufacturers. We also conduct research related to the development, manufacture, and testing of vaccines and related products. This work supports the

regulatory process and assists in establishing methods and standards to ensure the continued safety, purity, and potency of vaccines regulated by FDA. These include products prepared by genetic engineering, synthetic procedures, and other innovations in vaccine design. We have made the advancement of regulatory science at FDA a top priority. President Obama included \$25 million in his Fiscal Year 2011 budget request specifically for that purpose.

We provide our scientific expertise in guidance documents for industry, such as the recently finalized guidance document pertaining to the development of safe and effective cell-based viral vaccines. (See “*Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications*,” Guidance for Industry [February 2010]). In addition, we convene scientific workshops on emerging scientific and regulatory issues, where we share our knowledge of the latest science and seek input from other scientific leaders. We utilize an advisory committee comprised of a panel of outside independent technical experts from various scientific disciplines, whom we convene in a public forum to assist us in analyzing detailed scientific data and understanding its public health significance.

Some licensed vaccines (such as seasonal influenza vaccines made in eggs) are produced using technologies that have been in use for a long period of time. In general, such products have a lengthy and established track record of safety and effectiveness, which is an important consideration for preventative vaccines that are given to healthy individuals. FDA may consider the record of safe use associated with such “older” technologies, when the Agency evaluates the risks and benefits of products made using the latest innovations in vaccine design.

Representative John Shimkus

1. **In the past years you have asked drug companies to take drugs that are identified as being bad off the market. Have you not? Have they ever or has any company ever refused to do so?**

In cases where FDA reaches a conclusion that a drug's benefits no longer outweigh its risks and should no longer be marketed, FDA will ask the manufacturer to voluntarily withdraw the drug from the market. FDA has requested the voluntary withdrawal of about 50 drugs since 1976. The only instance in which the drug withdrawal was involuntary was the case of phenformin hydrochloride in 1979. The involuntary withdrawal procedure requires notice to the holder of the drug application and an opportunity for a hearing (section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act)).

In cases where a drug is either defective or potentially harmful, for example, due to problems with packaging, manufacturing, or contamination with foreign matter, FDA may request that a manufacturer voluntarily recall the product. (FDA does not have the authority to require that an adulterated, misbranded, or unapproved drug be recalled, although this authority exists for some FDA-regulated products, such as

medical devices and infant formula). A voluntary recall is when the manufacturer recognizes the problem and initiates action. While most manufacturers will undertake a voluntary recall promptly, in some cases, manufacturers will refuse to recall a product. In those instances, FDA issues a request for a recall, which is still not mandatory. A request for a recall is issued when FDA recognizes a problem but the company has not promptly initiated a voluntary recall. Since 2006, FDA has issued three requests for recalls. When a drug manufacturer does not comply with FDA's request for a recall, FDA uses press and other communication tools to notify the public of the potential risks. These actions were taken for the three situations noted above. After FDA issued press releases following issuance of the FDA Requested Recall action to the manufacturers, two of the manufacturers subsequently complied with FDA's recall requests. The third manufacturer refused to comply and, as a result, FDA seized the product that was on hand at the firm. A seizure action requires FDA to obtain a court order.

FDA believes that mandatory recall authority for drugs, modeled after section 111 of H.R. 2749, the Food Safety Enhancement Act, would enhance the Agency's ability to promptly address harmful drugs in the marketplace.

Representative Anna Eshoo

1. **The Food and Drug Administration Amendments Act of 2007 included a provision to give the FDA authority to require that television drug advertisements be reviewed by the FDA before airing.**

- How often has the FDA utilized its authority?
- What constitutes an “acceptable” drug advertisement?
- Does the FDA provide guidelines for drug companies crafting television advertisements?
- To your knowledge, have drug companies edited their advertisements base on the FDA's comments?
- How often do you reject advertisements based on objectionable content?

To date, FDA has applied its pre-review authority to three drugs. FDA is currently working to apply this provision to numerous other categories of drugs, and plans to issue guidance publicizing the categories of television ads that should be submitted for pre-review later this year.

An acceptable drug advertisement is one that complies with the FD&C Act and FDA's prescription drug advertising regulations, which require ads to be accurate, non-misleading, and fair and balanced in their presentation of risk and benefit information about the drug.

Drug companies must take the requirements in FDA's regulations into account when crafting television advertisements. We have published several guidance documents relating to prescription drug advertising that provide guidelines for drug companies as they develop their ads. In addition, the regulations allow companies to voluntarily

submit draft versions of ads to the Agency before the ads are publicly run. The Agency reviews these draft ads and provides companies with advisory comments, which inform them of any problems with the ads. This pre-review allows companies to correct problems before ads are aired or published. FDA is tracking the number of pre-reviews of drug advertisements through FDA-Track, available at: <http://www.fda.gov/AboutFDA/WhatWeDo/track/ucm206237.htm>.

Companies frequently edit their advertisements based on comments FDA provides through this voluntary advisory process. If FDA determines that a publicly disseminated ad is false or misleading, we can send the company an enforcement letter requesting that the company immediately cease the violative advertising. Companies also edit ads based on the objections FDA raises in these enforcement letters.

We comment on all the TV ads reviewed under the advisory process. This is not a pre-approval process, so we do not “reject” ads, but we do notify companies of regulatory problems with the ads and request revisions. We can also take enforcement action against misleading ads being publicly run. We sent 41 enforcement letters last year on false or misleading prescription drug promotion.

2. The Food and Drug Administration Amendments Act of 2007 included the reauthorization of and improvements to the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Can you comment on how these programs are working?

FDA has implemented several major changes concerning review of pediatric drug products as a result of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under FDAAA, FDA was provided increased authority to require pediatric studies and improve pediatric labeling. These programs are working well and have resulted in an increase in useful information for pediatric drug products. Some of the key changes include the following:

- FDAAA provides greater transparency and broadens the pediatric safety review process by requiring the Agency to apply the same processes for products studied under PREA and BPCA. There are three key areas in which this occurs:
 - (1) Pediatric studies under PREA are now subject to the same post-labeling, pediatric-focused safety reviews that have been used for BPCA, including review by FDA's Pediatric Advisory Committee. This change has resulted in a more comprehensive review of pediatric adverse events, in that it includes biological products.
 - (2) There is now a statutory requirement for inclusion of negative or inconclusive pediatric trial data in labeling. This clinical trial data, even if negative or inconclusive, is significant because many approved drug products are used “off label” in the pediatric population by medical

practitioners, as there is a lack of approved products for many pediatric indications.

(3) There is a required posting of the medical, statistical, and clinical pharmacology reviews of pediatric studies conducted to meet the PREA and BPCA requirements, regardless of whether the application is ultimately approved. Posting the reviews, instead of just summaries of the reviews, provides a better understanding of the clinical trial results and more substance as to the analysis of the data. It can also provide useful information to researchers and others involved in designing future pediatric studies. Given the limited number of pediatric trials that are conducted, this information can be particularly useful.

Following are some additional statistics (since enactment of FDAAA):

- Pediatric Advisory Committee (PAC) Review of Safety for Pediatric Products:
36 products have gone to the PAC pursuant to FDAAA as of March 22, 2010.
 - 17 pursuant to BPCA
 - 19 pursuant to PREA (including 7 biological products)
 - FDAAA Full Reviews Posted:
Total Number of Products Studied under BPCA = 37
Total Number of Products Studied under PREA = 47
 - FDAAA Labeling Changes Summary as of March 24, 2010 (Both BPCA and PREA) (N= 114)
 - New or Enhanced Safety Information – 23
 - Safety & Efficacy not Established in Pediatrics – 23
 - Expanded Age to Include Ages Previously not Included – 87
 - Specific Dosing Change/Adjustment – 4
 - FDAAA BPCA Labeling Changes Summary (N= 52)
 - Expanded Age to Include Ages Previously not Included – 29
 - New or Enhanced Safety Information – 12
 - Safety & Efficacy not Established in Pediatrics – 21
 - Specific Dosing Change/Adjustment – 1
 - FDAAA PREA Labeling Changes Summary (N= 62)
 - Expanded Age to Include Ages Previously not Included – 58
 - New or Enhanced Safety Information – 11
 - Safety & Efficacy not Established in Pediatrics – 2
 - Specific Dosing Change/adjustment – 3
3. The legislation also created the cross-division pediatric research consortium, or PeRC. PeRC provides consultation and review of pediatric plans, assessments, and studies across the agency. Can you comment on the progress of this consortium?

FDAAA required the creation of an internal FDA committee to carry out certain functions with respect to PREA and BPCA. FDA established this internal committee, called the Pediatric Review Committee (PeRC or the Committee), in October 2007. FDAAA required that, within 30 days after the enactment of FDAAA, this committee provide consultation to FDA Review Divisions on pediatric plans, assessments, deferrals, and waivers under PREA. This same committee was also directed to review all Written Requests issued under BPCA on or after the enactment of FDAAA.

PeRC plays an important role in providing an integrated and more consistent approach across FDA, from a scientific, legal, and ethical perspective, for pediatric drug product development, regardless of whether the product is studied under PREA or under BPCA. Previously, only products studied under BPCA were reviewed by the predecessor internal committee called the Pediatric Implementation Team (PDIT).

PeRC is an internal cross-Agency committee with members with critical expertise in not just pediatric matters but also in biopharmacology, statistics, chemistry, legal issues, pediatric ethics, and other scientific and medical specialties. Additionally, the PeRC includes individuals with appropriate expertise pertaining to particular products under review by the Committee. In addition, PeRC includes representatives (in addition to the pediatric ethicist) from the Office of Pediatric Therapeutics, who assist in collecting data, coordinating the safety reviews with upcoming labeling actions, and integrating information from the Pediatric Cluster, with the European Medicines Agency, in an effort to ensure optimal pediatric trial design and to prevent unnecessary duplication of pediatric trials.

FDAAA also required PeRC to conduct a retrospective review of information and actions taken in response to the Pediatric Research Equity Act of 2003. This report is publicly available at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM197636.pdf>

PeRC has held 140 meetings as of March 24, 2010. As of that date, with respect to PREA, PeRC had reviewed 145 deferrals, 143 pediatric plans, 117 pediatric assessments (the data submitted to fulfill the PREA requirements to provide data on the dosing, safety, and effectiveness in all relevant pediatric populations), and 334 waivers. With respect to BPCA, PeRC had reviewed 46 written requests.

Representative Mike Rogers

1. In FDAAA, I drafted language to require FDA to look into new technologies used for the identification, validation, tracking and tracing, and authentication of prescription drugs in order to secure the supply chain and protect patients from counterfeit products. What is the status of this report? What are the promising technologies FDA is exploring?

Section 913 of FDAAA requires that FDA ("the Secretary") "prioritize and develop standards for the identification, validation, authentication, and tracking and tracing of prescription drugs," which shall address promising technologies for achieving these goals. FDA is currently, and has been, exploring various existing, new, and emerging technologies that can be used for identification, validation, tracking and tracing, and authentication of prescription drugs. In order to find out more information to assist in that effort, in March 2008, FDA published a notice in the *Federal Register*, seeking comments on the following questions:

1. What are the radio-frequency identification (RFID) technologies, encrypting technologies, and nanotechnologies that are relevant? What are other relevant technologies?
2. Please provide information related to:
 - Strengths for identification, validation, track and trace, or authentication
 - Limitations for identification, validation, track and trace, or authentication
 - Costs of implementation and use
 - Benefits to the public health
 - Feasibility for widespread use
 - Utility for e-pedigree
3. Is the technology interoperable with other technologies? If so, describe.
4. What standards are necessary for supply chain use of the specific technology? What is the status of development of such standards?

FDA has reviewed and analyzed comments received in response to information requests about promising technologies and is using it to further inform the standards development required under section 505D of the FD&C Act (section 913, FDAAA), and implementation issues related to these standards. The types of technologies include, but are not limited to: RFID, encryption, holograms, bar codes, taggants, inks, and various types of nanotechnology.

The statutory requirement did not include a formal report to Congress related to the technologies for identification, validation, tracking and tracing, and authentication of prescription drugs; however, we welcome the opportunity to keep you updated on our efforts in this area.

FDA's ability to ensure product safety and address safety concerns would be greatly enhanced if Congress were to grant explicit authority to require a system that would allow for tracking, tracing, and authenticating drugs, devices, and tissues throughout the supply chain. Effective track-and-trace systems can make it more difficult for persons to introduce counterfeit or intentionally adulterated medical products into the U.S. market, make it easier to identify persons responsible for making a product unsafe, and facilitate the recall of unsafe products by more quickly identifying where a product is located in the marketplace.

2. I was interested to see that FDA recently issued Draft Guidance related to combating counterfeit drugs and the use of physical-chemical identifiers (PCIDs) or taggants. When do you expect the final guidance to be issued? Is this guidance meant to cover all forms of on-dose technology, including those that are not chemical identifiers and add nothing to the product? I am concerned that as drafted, the guidance could be perceived as an endorsement of taggants over other on-dose technologies. Can you assure us that all on-dose technologies will be addressed in the Final Guidance?

FDA is working to finalize this guidance. We are currently in the process of reviewing the comments received on the draft guidance to determine what changes may be needed. The final document will incorporate our current thinking on how best to address the risks in the use of taggants. New technologies are constantly being developed and the final guidance will be written to take into account the necessary flexibility in applying new technologies.

3. I am aware that FDA is developing a Risk Evaluation and Mitigation Strategy (REMS) for certain opioid analgesics. To date, opioid programs have focused on patient and prescriber education. While these elements will play an important role in the opioid-specific REMS, controlling the criminal elements, illicit diversion, and intentional misuse and abuse of opioid products will require a more specialized mitigation approach to track and trace products at the dosage level. What does FDA envision for the opioid-specific REMS and how this strategy will differ from current efforts to control abuse and misuse of these products?

Section 505-1 of the FD&C Act, as amended by FDAAA, describes the specific elements that may be included in a REMS. The elements are: a Medication Guide (or patient package insert); a Communication Plan; and Elements to Assure Safe Use. All REMS must include a timetable for assessment of the REMS.

In addition, section 505-1(f) lists the types of Elements to Assure Safe Use that a REMS may contain. The REMS may require that:

- Health care professionals who prescribe the drug have particular training or experience or are certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug may be dispensed to patients only in certain health care settings, such as hospitals
- The drug may be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results
- Each patient using the drug be subject to certain monitoring or
- Each patient using the drug be enrolled in a registry

FDA believes that establishing a REMS for opioids in accordance with our authority under FDAAA will reduce misuse, abuse, and accidental overdose, while still ensuring that patients with legitimate need for pain medications will continue to have appropriate access to them.

FDA may not be able to use the REMS to control the criminal elements and curb illicit diversion and intentional misuse and abuse of opioid products. However, other FDA efforts may more directly address these issues. Pursuant to section 505D of the Act, FDA is developing standards for identification, validation, tracking and tracing, and authentication of prescription drugs. In March 2010, FDA published a guidance entitled “Standards for Securing the Drug Supply Chain – Standardized Numerical Identification for Prescription Drug Packages (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125505.htm>). This guidance describes the standard for unique identification of prescription drug packages. FDA views this standard as an initial step to in the development of other standards and systems for further securing the drug supply chain. Many aspects of implementation of package level identification will take shape in the future as additional standards are developed. Although this track-and-trace system will not be implemented for several years, it could be used in the future as a means of reducing the criminal elements, diversion, and abuse associated with opioid products. Dosage level tracking and tracing is not being explored at the current time. In the meantime, FDA will continue to use its investigative and enforcement resources and work with DEA to curb criminal activity associated with opioid products.

We cannot describe the REMS at this point because FDA has not yet decided on the specific elements of the REMS. Once we have developed a proposed REMS, we will publish the proposal for comment, and plan to hold an advisory committee meeting to obtain expert advice and public input, before directing the sponsors to submit a REMS.

Programs such as these are extremely complex to develop, and FDA is actively working to ensure that the REMS is robust, effective, and will facilitate safe use of the drugs.

4. **Technology can provide a significant resource to FDA and law enforcement in addressing diversion. From an enforcement perspective, one of the most fundamental variables in a successful investigation is the product source information. Unfortunately, in the case of illegally diverted opioids, the information is minimal given that the medication is typically repackaged and the drug itself carries no information as to the intended site of distribution or origin. This lack of on-dose source information presents a challenge for government agencies seeking to mitigate diversion. Are you exploring the use of new track and trace technologies on the dosage form to control diversion and intentional misuse and abuse?**

FDA agrees that existing and emerging technologies can be useful in mitigating diversion, among other supply chain security threats. We are educating ourselves about various types of technologies, including on-dose technologies, as a means to

further secure the drug supply chain. Currently, however, we are focusing our efforts on tracking and tracing of prescription drug packages and pallets, as described in section 505D of the Act. FDA welcomes the opportunity to work with Congress to obtain explicit authority to require a system that would allow for tracking, tracing, and authenticating drugs, devices, and tissues throughout the supply chain.

Representative Phil Gingrey

1. **In the FDAAA legislation, I supported language to require FDA to look into new technologies used for the identification, validation, tracking and tracing, and authentication of prescription drugs in order to secure the supply chain and protect patients from counterfeit products. What is the status of this report? What are the promising technologies FDA is exploring?**

Section 913 of FDAAA requires that FDA "prioritize and develop standards for the identification, validation, authentication, and tracking and tracing of prescription drugs," which shall address promising technologies for achieving these goals. FDA is currently, and has been, exploring various existing, new, and emerging technologies that can be used for identification, validation, tracking and tracing, and authentication of prescription drugs. In order to find out more information to assist in that effort, in March 2008, FDA published a notice in the *Federal Register*, seeking comments on the following questions:

1. What are the RFID technologies, encrypting technologies, and nanotechnologies that are relevant? What are other relevant technologies?
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3. Is the technology interoperable with other technologies? If so, describe.
4. What standards are necessary for supply chain use of the specific technology? What is the status of development of such standards?

FDA has reviewed and analyzed comments received in response to information requests about promising technologies and is using it to further inform the standards development required under 505D of the Act (section 913, FDAAA) and implementation issues related to these standards. The types of technologies include, but are not limited to: RFID, encryption, holograms, bar codes, taggants, inks, and various types of nanotechnology.

Page 11 – The Honorable Henry A. Waxman

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FDA's ability to ensure product safety and address safety concerns would be greatly enhanced if Congress were to grant explicit authority to require a system that would allow for tracking, tracing, and authenticating drugs, devices, and tissues throughout the supply chain. Effective track-and-trace systems can make it more difficult for people to introduce counterfeit or intentionally adulterated medical products into the U.S. market, make it easier to identify people responsible for making a product unsafe, and facilitate the recall of unsafe products by more quickly identifying where a product is located in the marketplace.

2. **I was interested to see that FDA recently issued Draft Guidance related to combating counterfeit drugs and the use of physical-chemical identifiers (PCIDs) or taggants. When do you expect the final guidance to be issued? Is this guidance meant to cover all forms of on-dose technology, including those that are NOT chemical identifiers and add nothing to the product? I am concerned that as drafted, the guidance could be perceived as an endorsement of taggants over other on-dose technologies, can you assure us that ALL on-dose technologies will be appropriately addressed in the Final Guidance?**

FDA is working to finalize this guidance. We are currently in the process of reviewing the comments received on the draft guidance to determine what changes may be needed. The final document will incorporate our current thinking on how best to address the risks in the use of taggants. New technologies are constantly being developed, and the final guidance will be written to take into account the necessary flexibility in applying new technologies.

3. **Will the FDA be holding a public hearing on the guidance and, if so, will the administration ensure that all interested parties are invited to participate?**

FDA solicited public comment through publication of a notice of availability of the draft guidance in the *Federal Register* on July 14, 2009. Anyone can comment on any guidance at any time, but to ensure that FDA considers the comments before it begins work on the final version, they are encouraged to submit their comments within the deadline given in the *Federal Register* notice. As noted above, we are in the process of reviewing the comments received from interested parties, and at this time we do not anticipate scheduling a public hearing.

Representative Michael Burgess

During the debate on follow-on biologics in Congress, the focus has been on those products approved under the authority of the Public Health Service Act and proteins. There are, however, a subset of products approved under the authority of the Food Drug and Cosmetic Act (human growth hormone, insulin and low molecular weight

heparin) which are biologically derived for which the traditional process for approving generics should not apply. In an effort to deal with these types of molecules, pending legislation intends to create a pathway for follow-on biologics that includes a transition rule for some of these molecules. This is a recognition that these products are too complicated for a simple abbreviated new drug application (ANDA) route for generic approval. There remain, however, significant issues with regards to transitioning these products to a PHS approval pathway. Chairman Frank Pallone, on April 3, 2008 sent a series of 46 Questions to 36 different groups including FDA. One question addressed the transition directly.

The question read, "Should a newly created FOBs pathway include all biologics approved under the FFDCA and PHSA? FDA responded, "We believe that any proposal to transfer certain products now regulated under section 505 of the FD&C Act to section 351 of the PHSA should not be undertaken without very careful consideration of the legal and policy implications of such a change on the regulation of these products. For example, insulin products are proteins that have been regulated under the FD&C Act for more than 60 years. There could be significant regulatory implications if this product class were now to be approved or licensed and regulated under the PHSA. The Agency has not completed its consideration of this issue and would want to fully consider the potential implications of any specific proposal."

While citing insulins, the implication for other products falling into this scenario is the same.

We are interested in the following:

1. Has the FDA completed its review of the scientific, legal and policy implications of this change?
2. If so, what was the conclusion?
3. If not, what are the issues they are still considering and do they feel they have the appropriate authority to move these products to the new regime sooner?
4. Does the FDA feel it needs the full 10 year transition in order to prepare for the change?

Your questions concern the scientific, legal, and policy implications of transferring certain products currently regulated under section 505 of the FD&C Act to section 351 of the Public Health Service Act (PHS Act).

Under the recently enacted Patient Protection and Affordable Care Act (Public Law 111-148), FDA has been given the authority and responsibility to regulate biosimilar biological products, a newly defined class of medical products. Currently, FDA is carefully evaluating the newly enacted biosimilar provisions contained in the health care legislation to determine how best to implement these new provisions. Because we have not completed our review of the new law, including the provisions related to

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transferring certain products currently regulated under section 505 of the FD&C Act to section 351 of the PHS Act, we cannot answer your specific questions concerning these provisions at this time.

FDA established a cross-center working group that has been charged with the responsibility for establishing policies and procedures to implement the new provisions in a manner that best serves the public health. This working group is being led by Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), and Dr. Karen Midthun, Acting Director of CBER.

Representative John Dingell

1. **Would you please submit to the committee the number of people that you have at the different ports to ensure the safety and inspection of pharmaceuticals coming into this country?**

It is important to note that not all import control work occurs on the docks or at the border crossings. FDA staffs ports of entry in a variety of ways, depending upon geography and type and logistics of workload. Much of FDA's work in screening and examining import shipments occurs at locations other than ports of entry.

Entry data for all commercial shipments of FDA-regulated products are transmitted electronically by U.S. Customs and Border Protection (CBP) to FDA. Entry data for admissibility are routed to FDA offices based on the port of entry identified in the submission. Although some admissibility reviews are conducted at the ports, FDA employees conduct the majority of admissibility reviews of FDA-regulated products electronically at district or other field offices across the country.

Entry reviewers in the field offices examine shipment information electronically that are flagged for review based upon criteria placed in FDA's computer system, the Operational and Administrative System for Import Support (OASIS). Entry reviewers will schedule an examination and/or sampling of those products that appear to pose the highest risk or based on existing assignments. They allow the remaining products to proceed without physical examination.

The physical location where field examinations and/or sampling occur varies. Truck freight is often examined at a highway border port; however, many of these and the vast majority of ocean containers are examined and/or sampled at destination. This is permitted under section 801(b) of the FD&C Act, which states that articles may move to destination under a Customs bond to final destination, under condition that product is held and not distributed.

With regard to inspectional staffing of ports, below is some general information:

- Some ports are staffed onsite. For example, the New York District has investigators stationed daily at the Peace Bridge and the Lewiston Bridge in the port of Buffalo-Niagara Falls.

- Some ports are visited on a daily basis as needed, but the FDA inspectional staff is based at a central facility, which covers multiple ports within a metropolitan area. For example, San Francisco District covers entries through the ports of San Francisco, San Francisco Airport, Oakland, Richmond, Alameda, Crockett, and Martinez, among others, from the District Office in Alameda. Most of the import inspectional work is performed at consignee warehouses scattered throughout the Bay Area.
- Some remote ports have little FDA-regulated import traffic. These ports are rarely visited. Nonetheless, FDA reviews the entries for these ports as described above, and provides inspectional coverage onsite or at consignee locations, as needed. Examples of such ports would include Hilo, Kahului, and Nawiliwili-Port Allen in Hawaii, and Eastport, Bath, Bar Harbor, and Rockland in Maine.

Most ports are given inspectional coverage as required from the nearest FDA office during normal business hours, Monday through Friday. As mentioned above, many examinations and sample collections are performed not at the ports themselves, but at shipment destinations to which the goods travel under bond. There are a few major truck ports where FDA has inspectional staff during the evenings and weekends, such as the Ambassador Bridge in Detroit, Michigan and the Peace Bridge in Buffalo, New York.

Representative Joseph Pitts

1. **When the U.S. authorities interdict counterfeit drugs here in the United States, what occurs? What is done with those drugs?**

United States authorities encounter and interdict counterfeit drugs in different ways, including when they are offered for import into the United States or when discovered domestically. FDA relies on various enforcement tools to execute both regulatory and criminal responses when counterfeit drugs are encountered. In fact, these responses are not mutually exclusive, and there may well be circumstances under which both a regulatory and criminal response is appropriate.

FDA's import operations personnel may encounter counterfeit drugs at International Mail Facilities (IMFs) in addition to any U.S. port of entry during routine FDA screening/sampling operations of commercial entries. These encounters will most likely occur for products still in import status. FDA import operations personnel at IMFs review parcel contents for suspected counterfeit products by visually comparing the products in the parcel against known standards for U.S.-available products and packaging. If inspection of the shipment indicates a possible counterfeit, the information is provided to FDA's Office of Criminal Investigations (OCI) for potential follow up, as discussed further below. If OCI opens a criminal investigation, the counterfeit product may be seized as evidence. Otherwise, the products will be detained and ultimately refused admission into the United States by FDA's import operations staff. The exportation or destruction of the shipment is carried out under the direction of CBP.

FDA may also request sample collection for analysis of the product offered for import, and/or its packaging, by FDA's Forensic Chemistry Center (FCC). The determination to collect samples is made on a case-by-case basis, depending on the level of evidence supporting the suspicion of counterfeiting. Some type of laboratory analysis may be required to confirm that foreign shipments of drugs discovered by U.S. authorities at a port of entry are in fact counterfeit. FCC is FDA's lead laboratory for the analysis of counterfeit pharmaceutical products, including counterfeit active pharmaceutical ingredients (APIs), pharmaceutical dosage forms, and packaging. The FCC laboratory is accredited by the American Society of Crime Laboratory Directors/Laboratory Accreditation Board (ASCLD/LAB) and is staffed with experts on the analysis of counterfeit pharmaceutical products.

With regard to imported products, although FDA and CBP have authority to seize violative products, CBP currently does not have authority to destroy such products without first clearing resource-consuming procedural hurdles. FDA supports allowing CBP to destroy products in violation of FDA regulations that are valued at \$2,000 or less that pose a reasonable probability of causing a significant adverse health effect, with an opportunity for a hearing to be held after destruction. Such destruction would prevent repeated attempts to import products that have already been refused admission. FDA supports providing a post-destruction hearing in those cases, and a pre-destruction hearing in the case of articles valued at more than \$2,000 or that do not present a reasonable probability of causing significant health effects.

FDA counterfeit drug investigations may also originate from other sources, such as OCI's pro-active law enforcement activities, FDA inspections, private/trade industry information, the general public, regulatory partners, news media, and domestic/foreign law enforcement agencies. OCI will evaluate information received concerning counterfeit drugs for possible criminal investigation and, if appropriate, will make arrangements to obtain the counterfeit drugs for use in the investigation. In some instances, these investigations are conducted jointly with other law enforcement agencies, such as U.S. Immigration and Customs Enforcement (ICE) and the Federal Bureau of Investigations (FBI). Once a case is initiated, OCI Special Agents assigned to field offices throughout the United States conduct thorough and well-planned investigations, many times utilizing such investigative techniques as undercover investigations and surveillance operations. Counterfeit drugs are then used as evidence to support successful prosecutions through federal or state court systems, as appropriate. OCI maintains control of counterfeit drugs collected during an investigation and throughout the judicial proceedings. At the conclusion of trial, the evidence will remain in OCI's possession until the court authorizes its destruction.

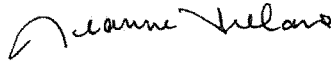
The FD&C Act authorizes FDA to seize counterfeit drugs, as well as their containers and labeling (See 21 *United States Code* (U.S.C.) 334(a)(2)). This authority has not been used in recent years, as most counterfeit cases are investigated (and product is seized as evidence) by OCI. However, once evidence is established to prove that a product is counterfeit, FDA, working with the U.S. Department of Justice, can file a

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complaint seeking forfeiture of the articles in U.S. District Court. If approved, the seizure is executed by the U.S. Marshals Service and court-ordered destruction, except in very unusual circumstances, would take place in the same judicial district in which the goods were originally located.

Thank you again for your interest in drug safety. If you have further questions, please let us know.

Sincerely,

A handwritten signature in black ink, appearing to read "Jeanne Ireland". The signature is fluid and cursive, with a large initial "J" and a stylized "Ireland".

Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosures

