# FDA'S FOREIGN DRUG INSPECTION PROGRAM: WEAKNESSES PLACE AMERICANS AT RISK

## HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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# FDA'S FOREIGN DRUG INSPECTION PROGRAM: WEAKNESSES PLACE AMERICANS AT RISK

**TUESDAY, APRIL 22, 2008**

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
*Washington, D.C.*

The subcommittee met, pursuant to call, at 11:00 a.m., in room 2123, Rayburn House Office Building, Hon Bart Stupak (chairman of the subcommittee) presiding.

Present: Representatives Stupak, Melancon, Green, Dingell (ex officio), Shimkus, Burgess, and Barton (ex officio).

Staff Present: Chris Knauer, John Sopko, Kevin Barstow, David Nelson, Kyle Chapman, Calvin Webb; Alan Slobodin, Peter Spencer, and Whitney Drew.

## OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. This meeting will come to order. Today we have a hearing titled "FDA's Foreign Drug Inspection Program: Weaknesses Place Americans at Risk." Each member will be recognized for an opening statement of 5 minutes. I will begin.

Today's hearing will once again explore the question of whether the Food and Drug Administration, FDA, is adequately regulating the overseas manufacture of pharmaceutical products. As this subcommittee has reported before, a significant and still growing quantity of pharmaceutical products used by Americans are now manufactured with ingredients obtained overseas from countries on almost every continent. With exact quantities and sources for these drugs difficult to determine, the general consensus is that at least 80 percent of all active pharmaceutical ingredients, APIs, used by U.S. manufacturers to produce drugs are imported. More importantly, much of this production occurs in regions that lack robust regulatory systems, such as China and India. China alone has more firms registered to export drugs to the U.S. than any other country, posing major challenges to the FDA. As was noted by former FDA Commissioner David Kessler in a major news production, I quote: "China is 'as close to an unregulated environment as you can get.' In fact, it is a lot like the U.S. was in 1906, he says—'That's why we developed an FDA.'"

The U.S. Food and Drug Administration is the Agency responsible for overseeing the safety and effectiveness of all human drugs

marketed in the U.S. As part of its effort to oversee the safety and quality of these products, FDA's policy is to physically inspect foreign establishments that ship drugs to the American market.

Last year this subcommittee asked the Government Accountability Office, GAO, to undertake a comprehensive audit of FDA's foreign drug regulatory system. The preliminary findings of that audit were presented at a hearing before this subcommittee on November 1st of last year. The GAO reported that a substantial lack of human and economic resources, weaknesses in databases in IT systems used by the FDA to track inspections and drug imports, and a lack of permanent operational support in foreign locations were major challenges facing the program. GAO also found that many of the FDA databases used to track foreign firms that export to the United States contain substantial material inaccuracies that have yet to be reconciled by the Agency.

More specifically, a lack of resources was determined to be a major factor undermining FDA's drug inspection program. For example, while current law requires FDA to inspect domestic firms once every 2 years, which FDA is managing to do roughly every 2.7 years, GAO reported that FDA only has enough resources to inspect foreign firms about once every 13 years. In China, one of the largest producers of active pharmaceutical ingredients for the U.S. market, FDA only inspects about 10 to 20 firms each year against an inventory of more than 700 firms. At this rate, the FDA can only inspect each Chinese firm about once every 30 to 40 years. Worldwide, GAO concluded that on an annual basis, the Agency only has enough resources to inspect about 7 percent of existing foreign plants, which amounts to inspecting one plant every 13 years. Given that these inspections are the most important tool the FDA has to ensure firms are meeting U.S. drug safety regulations, these rates are unacceptable.

FDA's IT systems for managing inspections and prioritizing risk was another major concern highlighted at the November 1st hearing. GAO testified that this system was antiquated, not designed for this purpose, and fraught with duplicative and inaccurate data. Such flaws made it difficult for the Agency to assess risk and prioritize inspections. Further, FDA could not determine how many foreign firms were subject to FDA inspections or where they were located. One database suggested that there were 3,000 foreign firms registered with FDA to market drugs in the U.S., and yet another database seemed to show 7,000 firms actually shipped products to the United States.

How can there be any confidence that the FDA is adequately regulating foreign drug firms when the FDA has no idea who's making what, where they are physically located, and when they were last inspected? These problems highlighted 10 years ago still plague the Agency today.

If the GAO and Subcommittee findings were not enough to demonstrate that the FDA's regulatory systems are broken, allow me to provide more evidence. In December of last year, a specially formed committee for the FDA submitted a comprehensive 2-year study entitled, "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology." This Science Advisory Board report assessed the Agency's ability to support a variety of

existing and future regulatory operations. The special subcommittee that concluded this review was comprised of nearly 3 dozen external experts who represent industry, academia, and other governmental agencies.

This subcommittee held a hearing on January 29th, 2008, to explore both the general concerns raised by the Science Review Board and their implications for food and drug import issues. The report advisors, including Chairperson Dr. Cassell, who will testify again today, provided alarming testimony regarding FDA deficiency in meeting its regulatory responsibilities. The panel is particularly troubled by the multitude of IT issues affecting the entire agency, including those related to foreign drug inspection program.

With regard to the scarcity of resources for conducting foreign drug inspections at the Agency, the report states: "Although approximately 80 percent of the active pharmaceutical ingredients used in our prescription drugs are imported from abroad, and foreign imports of drugs and active pharmaceutical ingredients were valued at more than $42 billion in 2006, FDA conducted only 361 foreign drug and biological product establishments in 2006. Only 32 field inspections were made in India and 15 in China, the two largest sources of pharmaceutical exports to the United States. Millions of shipments of FDA-regulated products are now imported into the country each year from foreign facilities that have never been inspected by FDA, and, with current appropriations, never will be."

The FDA Commissioner was present at the January 29th hearing. During his testimony the Commissioner agreed to consult further with the Subcommittee to explore ways to resolve the many problems identified in the Science Advisory Board report and address a multitude of concerns raised by the GAO, the Subcommittee, and others related to food and drug imports. Almost immediately on the heels of the January hearing, the FDA was quickly overwhelmed by the very type of crisis these reports and audits predicted would occur: contaminated heparin from China.

As we are now familiar, in late 2007 and early 2008, FDA began noticing hundreds of reports of adverse reactions to heparin, including vomiting, breathing difficulties, low blood pressure, and as many as 81 deaths. We would learn that tainted heparin was imported from China, and that the Chinese facility, Changzhou SPL, which made the active ingredient, had never been inspected by the FDA because of multiple internal failures. Laboratory testing revealed that a foreign ingredient called oversulfated chondroitin sulfate had somehow been added into the heparin production chain. While investigation into the origin of this contaminant continues, this tragic episode underscores the vulnerabilities in the current system used to regulate foreign drugs.

We have spent almost a year investigating the nature and extent of failures in FDA's foreign drug inspection program. After several hearings, the findings of the GAO, FDA's own Science Board, countless press articles, and the Subcommittee's own work, there are enough red flags to suggest to this Chairman, it is time to act and fix this program. GAO said it perfectly in last year's testimony, and I quote: "Until FDA responds to systemic weaknesses in the management of this important program, it cannot provide the need-

ed assurance that the drug supply reaching our citizens is appropriately scrutinized and safe." To date, FDA has been unable to assure the public these products are safe because they do not address the numerous systemic weaknesses many of us have identified. Because GAO and others will report today that many of the same problems we identified last year are still with us today, I can only conclude that American lives are unnecessarily being placed at risk.

I look forward to hearing from the Commissioner today. However, given the current nature of his agency's foreign drug inspection program, I think it is incumbent upon him to lay out a credible plan that demonstrates what steps the FDA has or will take to close these gaps and what resources or regulatory tools he needs to do the job.

Last year, this Nation's regulatory failure resulted in dead dogs and cats. This year, it has tragically led to the deaths of people. If we don't make rapid progress on fixing the foreign drug inspection program, the next melamine or heparin tragedy will soon be upon us.

With that, I next recognize the Ranking Member of the Committee, Mr. Shimkus from Illinois, for an opening statement.

Mr. SHIMKUS. Thank you, Mr. Chairman. I'd like to yield my time to the Ranking Member of the full committee, Mr. Barton, for an opening statement.

Mr. STUPAK. Mr. Barton, please, for an opening statement.

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

Mr. BARTON. Thank you, and I apologize for going out of order. I have another meeting upstairs that I'm going to go to after the statement and then I will come back down for the questions.

I want to commend Chairman Stupak and Ranking Member Shimkus for holding this hearing. It continues the bipartisan tradition of oversight work to ensure that the FDA is policing the safety of our drug supply. I want to commend Dr. von Eschenbach for attending, as he said he would when we had a hearing on this subject several months ago. It shows that he is a man who keeps his word and is willing to come before the Subcommittee when necessary.

We're all very concerned about the safety of our imported food and drugs. And we're even more concerned that many of those are coming from China, which has a spotty record of regulating its products which are sold for export. There is a long history of counterfeit products from China, shoddy manufacturing. Sometimes those shoddy manufactured products and counterfeit products cause real problems in our country. The American people deserve better, and there is something very, very wrong with our system if we can't decide on a collective basis, cooperative basis with the administration and the Congress, what to do about it.

This subcommittee has done outstanding work over the years in revealing the weaknesses in our current inspection program, both domestically and foreign. The risk from imported drugs has increased quite simply because the number of imported drugs have increased almost exponentially. And we haven't given the FDA the

resources to handle the increased scope of activity. And it is quite probable—if it's not probable, it's at least possible that the FDA's regulatory scheme has not been up to the task in terms of overseas inspections.

I was under the impression, until preparing for this hearing, that an active drug—a new active drug ingredient if it is from an overseas plant—had to have preapproval, and that required inspection. Apparently that's not the case because we've got evidence that the FDA has allowed foreign facilities to go uninspected or barely inspected. It would seem that that would be one change that we need to make and we need to make immediately.

Another issue before us is, I believe that the ability of the FDA to refuse products to come into this country needs to be put into statute. I thought again in preparation, not for this hearing but a previous hearing, that we had the statutory authority to give to the FDA that if they felt like a facility or particular drug or base ingredient wasn't safe, they could refuse its admittance to the United States market. Apparently that's not the case. It is an authority that the Secretary of Health and Human Services, Secretary Leavitt, has asked for. It is an authority that I support giving the FDA, and hopefully it's an authority we can put into statutory law on a bipartisan basis later this year.

It is clear that the FDA needs some new thinking in how to deal with the 21st century in the global commercial market that we have today. We don't have the luxury that we had even 50 years ago of just staying here, snug as a bug in a rug, in our home country, and blocking out the rest of the world in terms of drug imports and things like that. We have to come up with a system that makes sense both from an economic standpoint, from a regulatory and manpower standpoint, but also from a safety and efficacy standpoint. And that is the bottom-line purpose of this hearing.

The agency needs congressional approval to clarify its jurisdiction to warrant criminal conduct outside the United States that threatens the health and safety of the United States population—again, that's something I hope we can give the FDA in statutory authority later this year. The FDA needs a foreign inspection program with many, many more full-time inspectors overseas and with the availability to go into these foreign plants and conduct the inspections in overseas plants like they are allowed to conduct the inspections in domestic United States plants. Foreign inspections, unfortunately, are the neglected stepchild of the FDA's drug inspection program and that simply cannot continue.

I am told Commissioner von Eschenbach has several good ideas to share with us in this hearing about how to make those changes. Again, I want to welcome the Commissioner and welcome the panelists on the other panels. This is an important hearing and hopefully, while it's an oversight hearing, will lead to some legislative action that this committee takes to help remedy this problem in this Congress.

With that, Mr. Chairman, I yield back.

Mr. STUPAK. Thank you, Mr. Barton.

Mr. Dingell for opening statement, please.

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

Mr. DINGELL. Sir, I thank you for holding this very important hearing. Today we are here to again explore whether this administration is adequately able to protect American citizens from unscrupulous or incompetent foreign manufacturers of pharmaceutical products or whether they have the will to get the money and the resources necessary to do so.

Given the findings of this subcommittee of the recent disturbing events surrounding tainted heparin, I believe that FDA is clearly not up to the test, or cannot or will not undertake the reforms needed to protect Americans from this threat from abroad, or get the resources that they need to carry out the business that they are charged with. Indeed, they don't even tell us what their needs are to meet the challenges that are imposed upon them by their important responsibilities of protecting the health and safety of American people.

Now, let's summarize some of the Committee's key findings from its investigation so far. and then let us ask the Commissioner to defend the indefensible.

First, significant and growing amounts of pharmaceutical products are used by Americans that are manufactured overseas. At least 80 percent of all active pharmaceutical ingredients are now imported, much of it from countries lacking competent regulatory systems, such as China and India. Current U.S. law requires FDA to inspect domestic manufacturing firms once every 2 years. But there is no law requiring the same for foreign firms. And it is to be observed that FDA cannot and does not investigate foreign firms sending these kinds of substances into the United States.

While FDA is able to investigate and inspect domestic firms about once every 2.7 years, the inspection rate for foreign firms is once every 13 years or more. In fact at this time, FDA is able to only inspect about 7 percent of existing foreign firms shipping drug products to the United States annually.

Now, what does this mean? More than 700 Chinese firms are currently "registered" to export drug products to the United States. But FDA can only inspect about 10 or 20 of them per year. In other words, it would take FDA more than 30 years to inspect each Chinese firm a single time, assuming that no new firms are added to the list.

The information technology system, or IT system, that FDA uses to track and manage data on foreign manufacturers and the drugs they export to the United States is archaic and fraught with inaccuracies. As a matter of fact, FDA has pointed out to the Committee or to the public that a recent inspection of one of the firms involved in the heparin question was the wrong firm because it had a similar name.

FDA is unable to tell us how many foreign firms are subject to inspection globally, or where they are located. GAO reports that FDA cannot determine how many firms are exporting drugs to the United States. And we are imposing upon American manufacturers duties to produce safe, effective commodities and to do so under proper manufacturing practices. No such imposition is going on

with regard to foreign firms, simply because FDA can't inspect them or tell us that these requirements are being put in place.

The last time the Commissioner of Food and Drugs was here, he promised to return and give us the details of how he was going to fix this sorry mess. I hope that his testimony today will not resemble what he told the Senate appropriators last week, which appeared to be extraordinarily short on substance and heavy on bureaucratic buzz words. I'm hoping that the Commissioner will finally tell us what additional resources he needs.

The President's 2009 budget does little, if anything, to close the gap in foreign inspection rates. To this point, neither I nor the American people have any reason to believe that the administration is protecting us or is serious about protecting us from dangerous foreign-made drugs or raw materials from which these drugs are made. Frankly, until the Commissioner honestly tells the Congress what new regulatory tools are needed and what it will take to fix the broken IT systems, and how many personnel it will take to inspect foreign firms with meaningful frequency, I fear that we are going to continue to see contaminated products entering both our food and our drug supply, while FDA sits helplessly by watching calamities impend upon the safety and security of the United States.

This is an intolerable situation and this committee intends to address this with legislation this year. We hope that the Food and Drug Administration and this administration will do something about these matters. If they will cooperate and help, it will make it easier; but if they won't, we will do it to them anyway.

Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Dingell.

Mr. Shimkus for an opening statement, please, sir.

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

Mr. SHIMKUS. Thank you, Mr. Chairman. Today's hearing revisits the question of great and urgent importance to the American public and that is, What must the Food and Drug Administration do or be able to do to assure the safety of drugs in bulk drug ingredients imported into the United States? Part of the answer, of course, involves assuring a sufficiently robust foreign drug inspection program.

This committee explored the foreign drug inspection program in some detail at a hearing this past November. As was established at that hearing, the present situation doesn't make sense. We have an agency that has focused a majority of its facility inspections on domestic firms, when most of the facilities involved in supplying drug product to the American public are now situated overseas. A good portion of these facilities are in countries like India and China. And we have an agency that has not implemented the IT systems and informational tools to identify fully and rapidly the risks confronting us from abroad, let alone identify all the foreign facilities that should be subject to inspection.

We have already heard the numbers that show the imbalance in risk priorities, with most domestic firms inspected about every 2 years, about literally hundreds of foreign firms that have not seen

an inspection, if at all, in a decade. Clearly these priorities need to be brought closer into balance.

The Subcommittee also established that frequent surveillance inspections are important for assuring good manufacturing practices in foreign facilities. Good manufacturing practices and related safeguards over the supply chain reduce the risk that dangerous impurities in substandard products will turn up in U.S. medicine cabinets. Weak quality assurance safeguards have tragic effects. As Mr. Whitfield noticed in November, a bulk product that contains an impurity, something spot-testing may not detect, can cause injury or death to numerous people.

We saw this with Chinese imports of gentamicin in the late 1990s. We worry that the same may have occurred with heparin contamination in recent months.

The main reason for today's hearing is for the FDA Commissioner von Eschenbach to lay out for us his strategy for improving the Agency's foreign inspection program. He is here this morning to respond to findings by this subcommittee, and the GAO as well as the FDA Science Advisory Board. That panel's subcommittee report painted a picture of the FDA struggling to fill its public health mission. It described resource shortfalls, deficient information systems and structural problems at the Agency that we should address.

I very much appreciate the Commissioner's willingness to step once more into the Subcommittee's fire, but it is very important to hear its plans to address the problems we see. We will hear this morning some positive actions; but are these actions enough? Is the Agency using all the tools at its disposal to orient itself fully to the realities of foreign imports?

For example, we know there are informational tools at the FDA's disposal, such as pilot Predict system, that promise large advances in realtime risk assessment. Predict has been pilot-tested, but we have yet to see this deployed widely. Why the hold-up? And what does this say about the Agency's commitment to modernize? More disturbing is the Agency's policy to waive inspections, even in countries such as China, for reasons that have nothing to do with the facility risk or location. This ad hoc waiver may be driven by resource constraints, but it raises questions about the Agency's policy priorities as well.

As we move through the hearing today, I think it is important that first we develop good information about what the Agency is doing now to improve its information systems and foreign posture. We should learn how quickly it can bring some balance between its domestic and foreign inspection priorities. We should discuss what authorities FDA needs regarding overseas criminal conduct. This should help us improve our discussions about what Congress can do legislatively.

And second, as we discuss what more needs to be done, I'm hopeful we can also discuss where we want the Agency to be 10 years out. Do we want an agency structured as it is today, just with more people; or can we find some agreement that we need a smarter, more agile agency, using all the best and integrated information technology that can tackle the challenges of global commerce more cost effectively than the current model?

Mr. Chairman, the Subcommittee has done great work to identify the Agency's weaknesses as they exist today. Let us gather some facts and perspective to develop a vision for this agency's future as well. I yield back the balance of my time.

Mr. STUPAK. I thank you.

I want to ask Mr. Melancon for an opening statement, please.

Mr. MELANCON. Thank you, Mr. Chairman. I'm going to waive an opening statement and reserve my time for future use. Thank you.

Mr. STUPAK. Mr. Burgess.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BURGESS. Thank you, Mr. Chairman, and thank you for holding this hearing today. I think it's timely and, as the heparin story unfolds, we have no choice but to be more proactive in our safety measures abroad.

Mr. Chairman, I'm a physician before I came to Congress, and I know that I have to trust what I'm prescribing for my patients. I have to trust that it is not adulterated, that it has not been mislabeled. I have to trust that someone with criminal intent has not adulterated the medication. The reason I trust the medicine is because the Food and Drug Administration approved it.

If it is acceptable that we do not know exactly who manufactured the ingredients of the drug, or if those ingredients are safe or not, or if the factories have even been inspected, then that whole system comes into question.

Pure and simply, doctors rely on the Food and Drug Administration to approve drugs that keep the American public safe, and they've done a great job over the years. That safety is generally stipulated when a patient comes into a doctor's office and a prescription or treatment is recommended.

Today, we are very fortunate to have a physician at the helm of the Food and Drug Administration. Therefore, he can relate to my concerns about the trust that physicians place in this Federal agency. I certainly would like to thank Dr. von Eschenbach for once again appearing before us to continue this important dialogue on the Food and Drug Administration's inspection program.

In addition to Dr. von Eschenbach's testimony, we will also hear from the Chair of the Science Board. When we had our hearing earlier this year on the report, I was very disturbed at some of the findings. Dr. Cassell's testimony today will hopefully shed more light on how the report relates to a Food and Drug Administration foreign drug inspection program. With the significant increase in imports, I think this program should be one of the most crucial programs we have at the Food and Drug Administration. So, Dr. Cassell, thank you for being with us today as well.

And I would be remiss if I did not welcome Dr. William Hubbard. You have provided this committee with great insight, and I thank you for your commitment to making what I believe is arguably the most important Federal agency in the United States better and stronger.

We heard the Chairman—I'm sorry, the Ranking Member of the subcommittee—Ranking Member of the full committee, rather, talk about the ability to stop dangerous food imports from entering our

country. H.R. 3967, the Imported Food Safety Improvement Act that was introduced earlier this year, that bill came largely as cooperation and instruction and advice from Al Hubbard, Dr. Hubbard, to our office. And we need the same authority now for the active pharmaceutical ingredients that are manufactured in other countries coming into our country.

Mr. Chairman, we are here today to better understand the Food and Drug Administration's foreign drug inspection program. And, unfortunately, we all realize the Food and Drug Administration has real problems in ensuring that our Nation's food, drugs, and devices are safe and effective. What is not clear is how the Agency has responded to these shortcomings, and how effective these measures have been, and how Congress could actually be helpful in getting the FDA to make the necessary changes.

According to the GAO report that we will hear about today, some changes are being made as to how the FDA handles drug importation. But these changes will require widely invested resources and firm leadership in order to have the accomplishments that we all so much desire.

The former Speaker of this House of Representatives, Newt Gingrich, says, time and time again, real change requires real change. New technology is desperately needed to help integrate the databases and modernize the recordkeeping.

Apparently there is talk of starting FDA field offices overseas, a measure that I would likely support. However, the mission of these new offices is still not clear in establishing that clarity should be crucial for receiving the support of this subcommittee. Meanwhile, we are still consuming drugs from factories that have never been inspected, are possibly completely unknown, and we have people dying from these affected medicines.

The heparin story is still evolving, Mr. Chairman. It is interesting that no test, no test available would have detected the hypersulfated chondroitin present in the contaminated product that came into this country, the very contaminant that is thought to cause the adverse heparin reactions.

With that, the FDA is trying to improve, and I believe is trying to improve, under the leadership of Dr. von Eschenbach. Change and progress is occurring, but these improvements require resources that have been denied for many years.

Now, the Chairman of the full committee asked a question, a rhetorical question, I assume: What additional resources the FDA needs to protect the American people. He questioned the administration's sincerity about protecting the American people. I think realistically anyone who has watched this full committee over the past several weeks would have to wonder about congressional intent and whether or not that's also suspect, with the ill-advised bill we had a few weeks ago to have the FDA take on an entirely new venture to regulate tobacco. And the lead editorial in today's Wall Street Journal finishes with the observation, "congressional priorities are rarely so grotesque." And I would agree with that.

Mr. Chairman, it is not just dollars. We've heard from the Science Subcommittee the personnel report, and the training of those personnel are important. The policy and procedures within the Food and Drug Administration are critical, the lack of informa-

tion technology infrastructure prevents—truly prevents the development of a 21st century system that's needed to protect Americans. And after all, at the end of the day, that's what we are all after, providing Americans with the protection that they have grown to give, that knowledge that they have grown to accept from the Food and Drug Administration that that protection is just a given, it is just assured.

With that, Mr. Chairman, I yield back the balance of my time.

Mr. STUPAK. I thank the gentleman.

Seeing no other members, we will call our first witness.

That concludes the opening statements by members of the subcommittee, and I call our first panel witness to come forward. Our first panel, we have the Honorable Dr. Andrew von Eschenbach, Commissioner of the Food and Drug Administration. It is the policy of this subcommittee to take testimony under oath. Please be advised that you have the right under the rules of the House to be advised by counsel during your testimony. Do you wish to be represented by counsel?

Dr. VON ESCHENBACH. No, sir.

Mr. STUPAK. OK.

[Witness sworn.]

Mr. STUPAK. Let the record reflect the witness replied in the affirmative. Doctor, you are now under oath, we will hear your opening statement. You may submit a longer statement for inclusion in the record. Commissioner, your opening statement, please.

**STATEMENT OF ANDREW C. VON ESCHENBACH, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, WASHINGTON, D.C.**

Dr. VON ESCHENBACH. Thank you very much, Chairman Stupak, Ranking Member Shimkus, members of the Committee, and Chairman Dingell. Over the past 2½ years, everytime I have appeared before this committee my message has been the same: The FDA is immersed in a rapidly and radically changing world and we must make radical and rapid changes if we are going to continue our record of excellence as the world's gold standard regulatory agency for food and medical products for both people and animals.

I have consistently endorsed the fact that this would require additional resources, and over three budget cycles have presented requests for those additional resources to the Administration and to Congress. Most importantly, I've presented to this committee plans and proposals to use current and future resources wisely and strategically to achieve our mission to protect and promote the health of every single person in the country and, in fact, around the world.

Globalization, increased product complexity, and other market developments, are placing tremendous strains on our import safety system. These trends are not new and were anticipated years ago in a report by the GAO. The agency's response has been deliberate, but nowhere adequate in proportion to the growth of the challenge.

[Slide shown.]

Dr. VON ESCHENBACH. The first slide I share with you just demonstrates the volume of FDA-regulated products that are entering into this country. The data demonstrate that inspection at our bor-

ders for this volume of products could never be an adequate barrier that would assure protection to patients and consumers.

[Slide shown.]

Dr. VON ESCHENBACH. The next slide shows the number of establishments producing drugs outside the United States for import and, just looking at drugs, there are over 1,300 sites. And you can multiply this many-fold if you consider active pharmaceutical ingredients, biologics, medical devices, and generic drugs. No matter how we arrived at this point, if we address the challenges of this reality, the solution is not simply to just do more of what we have done in the past, but we must do things differently.

[Slide shown.]

Dr. VON ESCHENBACH. The next slide indicates that FDA must not just be a gatekeeper, but must be involved across the full life cycle of the products that we regulate, from their very production to consumption, by imposing strategies that encompass prevention, intervention, and response across the entire supply chain, both domestic and foreign.

As you mentioned this morning, Mr. Chairman, at the core of this systems approach to this total engagement and product life cycle is the need to create a state-of-the-art information technology infrastructure with data management systems that are capable of acquiring the complex and diverse information from multiple sources with integration and analysis of that information that defines risks, and targets appropriately FDA's regulatory resources and actions.

At the last hearing I discussed with you our vision for our enhanced information technology infrastructure and the progress we are making along a trajectory toward a total renovation of this infrastructure by 2010. But information management that provides comprehensive information about the regulated product is only one component of what is required. We must assure that quality is built into these products at the very source of production, and that all parties involved in the entire supply chain are held accountable for maintaining that quality. FDA must be proactive.

In that regard, today, I describe to you a major initiative of quality assurance: FDA's Beyond our Borders Initiative. This addresses imported products with a systems-based approach to the systemic problem of the Agency's regulation of food, cosmetics, and medical products. The initiative includes a number of broad activities, including increased collaboration with foreign regulators, use of third parties to provide information about regulated industry compliance with FDA standards, and also providing additional direction to the regulated industry for their global activities.

Beyond our Borders presents and builds on the very extensive and successful collaboration we have already established with foreign counterparts, including more than 70 cooperative agreements and 30 confidentiality agreements with trusted foreign regulators, many of which provide the possibility of sharing inspection reports. These relationships provide a strong foundation for more extensive collaborations to prevent failure and quality, to intervene earlier when standards are not being met, and respond more rapidly and efficiently to signals of adverse outcome.

The increasingly global nature of product development and production requires our continuous and intensive interaction beyond our border. This plan includes the establishment of FDA offices in China, India, Latin America, Europe and the Middle East. I have been engaged in direct discussions in each of those areas to obtain support and a welcome for a U.S. FDA presence, and that progress is well underway, especially to establishing our first office in China.

FDA can rely in part on these efforts in making important risk-based decisions regarding imports. Permanent overseas offices, especially in China, will allow greater access for FDA inspectors and, very importantly, greater interactions on an ongoing basis between FDA staff and Chinese officials and manufacturers to help assure that products that are being shipped to the United States meet FDA standards for safety and manufacturing quality.

Another component of Beyond our Borders leverages private sector resources. As recommended in the President's action plan for import safety, FDA is pursuing expanded use of third-party certification by foreign producers to verify compliance with U.S. safety and security standards with FDA oversight and verification. These third parties can include foreign government agencies as well as independent agencies accredited by the FDA. And they can provide helpful information about compliance with FDA's requirements. FDA certification will not supplant our inspectional responsibilities or our regulatory activities, but will simply complement them and expand our affect.

To help increase information about foreign facilities, we will also engage external nongovernmental organizations with foreign offices to conduct onsite verification of registration data, product listing information, and the information so necessary in our ability to understand the source of these products. We would also be visiting foreign firms and verifying and documenting that information on a continuous ongoing basis. Assisting foreign regulators to be able to understand, implement, and embody FDA standards is another essential component of this initiative to build capacity beyond the FDA to a global effort at product safety.

My written testimony about our prevention intervention response strategy provides more specific information about Beyond our Borders Initiative and our efforts are underway to enhance our oversight of imported products. Important of these is the request of new authorities that will help ensure that foreign manufacturers of drug products are in compliance with U.S. law.

We have requested Congress to provide statutory authority for FDA to require certification by third parties, in certain circumstances that incoming products must meet U.S. importing standards; that we can refuse admission of products for which FDA encounters undue delay, limits, or denials of access for inspection of foreign manufacturing sites; that we have the authority to expedite destruction of certain unsafe medical products and authority to seek asset forfeiture remedies for criminal offenses regarding fraudulent or counterfeit products.

I appreciate the opportunity to once again be with you today, and I look forward to answering your questions about the details of these proposals that will enhance and strengthen FDA's ability to

ensure Americans of the quality of the products they consume, irrespective of where they are made.

Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Commissioner.

[The prepared statement of Dr. von Eschenbach follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

**STATEMENT OF**

**ANDREW C. VON ESCHENBACH, M.D.**
**COMMISSIONER OF FOOD AND DRUGS**

**U.S. FOOD AND DRUG ADMINISTRATION**

**BEFORE THE**

**SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS**

**COMMITTEE ON ENERGY AND COMMERCE**

**U.S. HOUSE OF REPRESENTATIVES**

# "FDA Actions to Improve Safety of Medical Products with Foreign Components"

**APRIL 22, 2008**

RELEASE ONLY UPON DELIVERY

**INTRODUCTION**

Mr. Chairman and Members of the Subcommittee, I am Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs. Thank you for the opportunity to discuss the U.S. Food and Drug Administration's (FDA or the Agency) progress in responding to the challenges created by drugs for the U.S. market that are either fully manufactured overseas or that are manufactured in the U.S., but contain foreign components. FDA's mission is to ensure that safe and effective drugs are available to patients, regardless of where they are produced. Globalization, increased product complexity, and other market developments are placing tremendous strains on our import safety system. The multiple and complex changes facing us in the 21st century pose challenges for our import safety system that we are working to address. In my testimony today, I would like to outline the Agency's systems-based approach to address these challenges.

**21ST CENTURY CHALLENGES TO OUR DRUG DELIVERY SYSTEM**

Any entity that intends to import drugs or drug components into the U.S., in compliance with the Federal Food, Drug, and Cosmetic (FD&C) Act, must ensure, among other things, that the drug meets a number of manufacturing quality and product labeling requirements. In the FD&C Act, Congress created a "closed" distribution system for domestically and internationally manufactured drug products to help ensure the domestic supply is safe and effective. In this "closed" distribution system, all prescription drugs, whether manufactured in the U.S. or abroad, must be approved by FDA as "safe and effective" for their intended use prior to marketing in the U.S. In order for a product to be determined "safe," it must be manufactured in ways that assure the continued quality of the product with each new batch or production quantity and that assure that changes in the manufacturing processes do not result in changes to the product's clinical safety and

efficacy profile. Because of this, FDA prescription drug approvals are manufacturer-specific and product-specific, and include many requirements related to the product's manufacture, such as manufacturing location, formulation, source and specifications of active ingredients, manufacturing controls, the container/closure system specifications, and product labeling. Facilities, be they domestic or foreign, that manufacture drugs for the U.S. market must meet FDA's current good manufacturing practice (cGMP) requirements.

FDA's regulation of drug products is considered one of the international "gold-standards," and our goal is not only to maintain that standard but continually strive for improvement. We do not, however, operate in isolation, but instead in the context of a rapidly-evolving world in which local markets deliver products produced, in whole or in part, anywhere in the world. The domestic production-to-consumption system of the past is changing to reflect the globalization trends of today. Source materials and production sites can be oceans apart. The complexity of products and their components grows alongside an industry that is dispersed and decentralized. The rate of imported FDA-regulated goods has grown dramatically over the last decade. This trend will continue, presenting FDA with the significant challenge of regulating a lengthening supply chain with a shortened distribution time. These changes are challenging the Agency's import safety system in the 21st century.

**FDA'S SYSTEM-BASED APPROACH TO A SYSTEMIC PROBLEM**

FDA is responding to these changes by building systems that better identify and prioritize potential risks all along the product's life-cycle. This involves significant challenges with regard to imported products. FDA needs a more continuous stream of information about the risks posed along the entire life-cycle of imported products, and the ways in

which manufacturers, transporters, importers, and distributors are addressing those risks. Such information will allow FDA to target its resources in the most efficient manner to best protect public health.

To facilitate these and other import safety needs, the President issued an Executive Order on July 18, 2007, which established the Interagency Working Group on Import Safety (Working Group). The Working Group recently presented the President with an Action Plan for Import Safety. FDA's implementation of the Action Plan addresses the needs of a globalized economy, which demands heightened regulatory interoperability, information exchange, and cooperation with foreign regulatory partners, especially on product quality and enforcement matters. The following describes FDA's life-cycle approach – based on this Action Plan - to improving the compliance of foreign drug manufacturers with U.S. regulations. This life-cycle approach provides a science-led, risk-based system to help keep Americans safe by *preventing* harm before it can occur, enhancing our *intervention* methods at key points in the distribution system when risks are identified, and by strengthening our ability to *respond* immediately when harm has occurred or is imminent.

**Preventing Harm Before It Can Occur**

The U.S. border must become one of several integrated checkpoints to verify that imported products comply, including in their manufacture, with U.S. health and safety requirements. In other words, FDA must further shift from "gate-keeper" to a stronger and more comprehensive import safety authority. Imported drugs and devices must be safe and effective and must meet all applicable FDA standards *prior* to reaching U.S.

ports-of-entry. FDA is taking many actions to prevent harm to the American consumer before medical products reach our border.

*Maximizing Foreign Prescription Drug Pre-Approval Inspections.* Prior to the approval of a new drug application (NDA) or abbreviated new drug application (ANDA), FDA determines that the manufacturing processes for the active pharmaceutical ingredients (API) and finished dosage form of the drug are adequate to preserve the drug's identity, strength, quality and purity. FDA performs hundreds of foreign prescription drug manufacturing inspections per year. Most of these foreign inspections are pre-approval, cGMP inspections designed to evaluate the capability of manufacturing facilities to generate a safe and high-quality product. FDA conducted more foreign drug inspections in fiscal year (FY) 2007 (498) than any other prior fiscal year in the Agency's history. This is a marked increase over the past few years as well, compared to 374 in FY 2004, 370 in FY 2005, and 342 in FY 2006. Exercising FDA's regulatory authority is challenging. In some countries, we need authorization from that government to enter and inspect facilities. In some cases, the U.S. Department of State issues travel alerts and travel warnings that require FDA to appropriately take special precautions to ensure the safety of our investigators in these locations.

Foreign inspections are more costly than similar inspections of domestic facilities because of travel costs and special needs associated with travel abroad. There are approximately 800 FDA investigators trained to conduct foreign inspections in all program areas and 335 specifically for the drug program area. FDA relies on assistance from the firms' U.S. agents and representatives to translate if needed and help with logistical challenges that arise in traveling to foreign facilities. In certain circumstances, FDA can obtain help in these areas from U.S. Embassy and HHS personnel stationed in

the country in which an inspection is scheduled. While FDA is committed to increasing the number of foreign inspections.

*Beyond Our Borders Initiative.* FDA's Beyond Our Borders Initiative is a systems-based approach to the systemic problem of the Agency's regulation of food, cosmetics, and medical products. The Beyond Our Borders Initiative includes increased collaboration with foreign regulators, use of third parties to provide information about regulated industry compliance with FDA standards, and providing additional direction to regulated industry for their global activities. This initiative will be financed with existing FY 2008 resources and the President's FY 2009 Request.

FDA has in place more than 70 cooperative arrangements with foreign counterparts. Under the leadership of Secretary Leavitt, for example, HHS signed a Memorandum of Agreement (MOA) with the State Food and Drug Administration of the People's Republic of China in December 2007 to enhance the safety of drugs and medical devices imported into the U.S. from China.

*Sharing Foreign Inspection Reports.* In addition to our cooperative agreements and arrangements, FDA now has over 30 confidentiality arrangements with trusted foreign counterparts, many of which provide for the possibility of sharing inspection reports, redacted of proprietary information. FDA intends to increase the use of these arrangements to obtain useful inspectional information that can help FDA make more informed judgments in the prioritization of foreign inspection activities. Through our negotiation of specific bilateral work plans with other trusted foreign counterpart agencies, we intend to explore opportunities to acquire useful inspection information from established, trusted foreign agencies with which we can establish appropriate

confidentiality arrangements. For example, the European Union (E.U.)-U.S. Bilateral Technical Working Group on Medicines Quality and Manufacturing is focusing on utilizing and leveraging resources through the exchange of inspectional planning data and inspectional observational data for plants in the U.S. and E.U. and in other countries inspected by either the E.U. or the U.S.

*Foreign Presence.* FDA and HHS leadership, the Department of State, and the U.S. Ambassador to China have committed to establishing an FDA office in China. Along with the important MOA signed with two FDA counterpart Chinese agencies, permanent FDA positions in China are a significant step toward ensuring access to safe food, drugs, and medical devices in the global market. FDA's efforts will build stronger cooperative relationships with the FDA's counterpart agencies in China, enhance technical cooperation with these agencies, and foster development of information flow from a regulatory system in China. FDA can rely in part on these efforts in making its risk-based import decisions. The permanent overseas office in China will also allow greater access for FDA inspections and, very importantly, greater interactions between FDA staff and Chinese manufacturers to help assure that products that are shipped to the U.S. meet FDA standards for safety and manufacturing quality.

In addition, an FDA delegation visited counterparts in India to begin conversations to establish appropriate counterpart collaborations in that country. By the end of this year, we are hoping to have established in-country FDA presence in China and limited engagement in India.

*Providing for Certification by Third Parties.* Another component of the Beyond Our Borders Initiative leverages private sector resources. As recommended in the President's

Action Plan for Import Safety, FDA is pursuing expanded use of third party certification to verify compliance with U.S. safety and security standards. These third parties can include foreign government agencies and independent entities who have been accredited by FDA or by an accreditation organization recognized by FDA. Such third-party certifications can provide FDA with helpful information about a firm's compliance with FDA requirements. This certification would not supplant FDA inspectional or other regulatory activities, but would complement them. This information will aid FDA in prioritizing and targeting its compliance and inspection resources toward high-risk situations. The China MOA, for example, includes a provision for a registration program and working toward a system that will enable the Chinese government to certify the status of Chinese firms that manufacture active pharmaceutical ingredients (API) and other components of finished drug products. To support the Chinese registration program, and efforts to work toward a certification program, agencies from the two countries will conduct training programs and activities to cover topics such as inspection methods and clinical trials to ensure safety; will discuss each country's development of relevant technical guidance documents, regulations, and laws. In addition, the Agency is developing a pilot program that would reduce the delay for firms that take pro-active measures when they import finished drug products and APIs.

*Implementing Foreign Vendor Registration Verification.* To help increase information about foreign facilities, FDA also plans to engage external, non-government organizations with foreign offices to conduct on-site verification of the registration data and product listing information of foreign firms shipping regulated products to the U.S. This process would include visiting foreign firms, and verifying and documenting that they exist and manufacture the products that FDA records indicate they export to the U.S.

*Providing Technical Assistance.* Another essential element of the Beyond Our Borders initiative focuses on helping foreign regulators understand FDA standards. To help ensure compliance with FDA laws and regulations, FDA provides technical assistance to counterpart foreign regulators and to foreign industries that engage in trade with the U.S. to help ensure understanding of, and compliance with, U.S. safety and other regulatory requirements. A significant proportion of the U.S.' increased trade volume comes from developing economies. Such countries need information and expertise to help them oversee production of FDA-regulated products to ensure that they meet the applicable legal requirements and can be imported into the U.S. FDA is seeking to provide additional technical assistance to raise the confidence we can all have in the safety of these products.

*Issuing Good Importer Practices (GIPs).* FDA also plans on issuing guidance on GIPs to help the importing community take appropriate steps to ensure the safety of their products.

**Enhancing Intervention At Key Points**

*Building A Modern IT Infrastructure.* Upgrading FDA's IT systems is one of my top priorities. We expect these improvements will help to target our intervention efforts related to foreign firms. Today, foreign producers must register with FDA before shipping to the U.S. However, because for most firms there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S. Others may register and then discontinue shipping without any notice to FDA. These practices create uncertainty about the precise number of FDA registered firms among which to

target inspections, often necessitating secondary data-source checking. Importers must also provide information about the product being imported and its manufacturer. However, our systems do not yet have the capability to automatically verify the accuracy of all of the information submitted. We are working on more effective and efficient solutions to ensure the accuracy and validity of the data in our registration and import information technology (IT) systems. These IT initiatives are within existing FY 2008 resources and the President's FY 2009 Request.

FDA's Bio-informatics Board (BIB) is addressing this issue for FDA. The BIB, in-part, focuses on the issue of establishing accurate information on firms and their products. We are actively seeking other means to identify duplicate entries, such as those caused by variations in how name and address information is provided. FDA plans to enhance its IT systems in ways that will enable the Agency to better utilize risk-based information from the entire life-cycle of imported products. Many of these improvements will be implemented in the next two years; implementation of a few will extend beyond 2010. These projects will improve data bases, enhance interoperability of systems within the Agency and among other regulatory agencies, and provide better analytical function to assess and control risk.

For example, the Mission Accomplishment and Regulatory Compliance Services (MARCS) program manages the integration, re-engineering, and enhancement of the legacy systems that support FDA field activities. These systems include the Operational and Administrative System for Import Support (OASIS) and other components which support import processing. Improvements include replacing the current process that screens import entries; giving investigators faster access to product information in FDA

databases; improving sample collection/tracking on both desktop and mobile platforms; and developing a broker information center to allow Customs Brokers to quickly exchange information with import reviewers.

In addition to MARCS, FDA is working on a number of related projects that will improve import safety. These include working closely with Customs and Border Protection (CBP) to ensure that its planned Automated Commercial Environment (ACE), a component of the International Trade Data System (ITDS), will provide the functionality long sought by FDA with respect to entry data submitted by import brokers and filers. FDA will also complete its Unified Registration and Listing System (FURLS), an electronic integration of the registration and listing systems currently maintained in the individual Centers. This unified system will allow the Agency to have a more complete and accurate database of FDA-regulated establishments.

Another IT initiative that has the potential to make a dramatic change in FDA's business practices is PREDICT, an automated entry screening system that incorporates relevant risk data from all points in the import life-cycle, including data currently outside FDA databases, to predict and prioritize the highest risk import entries. A pilot test of the PREDICT prototype system was conducted by FDA during the summer of 2007. The pilot was limited to seafood imported through a small number of ports in southern California. Our plan is to expand the prototype to include all food products and then to include all other FDA-regulated commodities.

*Increasing Surveillance Inspections.* In addition to pre-approval inspections, FDA conducts surveillance inspections of domestic and foreign manufactures and uses a risk-

based priority model to determine which facilities may pose a risk to the American consumer. Given the need to use resources for foreign surveillance inspections as efficiently as possible, FDA staff must consider a number of elements in making a risk-based priority determination. In part, these elements include: the complexity of the dosage form coming to the U.S. from the foreign country, the date the facility was last inspected, the compliance history of the firm, the shipping volume and history, and information from the local regulatory authorities regarding the manufacturing quality and regulatory status of the enterprise. As mentioned above, FDA is conducting more inspections than ever and we are committed to conduct more surveillance inspections in an effort to help ensure compliance with cGMP standards and prevent product problems.

*Holding U.S. Manufacturers Accountable.* The President's Action Plan for Import Safety outlines several action steps intended to help ensure that importers are aware of their responsibility for safe and effective medical products. U.S. manufacturers also have a responsibility to ensure the safety of foreign-manufactured ingredients used for their finished dosages. U.S. manufacturers of finished dosage forms of drugs that import APIs or other components from abroad must examine and test those ingredients before using them in their drug products under cGMP. FDA may inspect a firm's foreign facilities and/or their domestic facilities to determine if the manufacturing facility meets the Agency's quality standards. In addition, FDA inspections routinely evaluate manufacturers' testing and controls of ingredients and supplies. If, during a domestic or foreign inspection, FDA determines that an imported API fails to meet specifications or is not manufactured using cGMP, FDA has several options. FDA may issue an import bulletin instructing staff to test future shipments. The determination may also support an import alert by means of which FDA could detain future imported shipments. Finally,

such a determination may result in delay or denial of approval of the product's U.S. marketing authorization.

**Rapid Response to Emerging Safety Risk & Product Problems**

When a health threat does emerge with an imported product, FDA must be ready to take immediate action. Above, I have described many ways the Agency is operationalizing its approach to verifying compliance to reward good behavior. At the same time, FDA must respond authoritatively when we find bad actors in the marketplace.

*Making the Border an Integrated Checkpoint.* FDA works with CBP at the border to refuse admission to those products offered for import that appear to violate the FD&C Act. FDA screens 100 percent of the imported APIs and finished form drugs entering the U.S. to determine whether the product is going to the corresponding facility in the approved NDA and whether that facility is registered and listed. In addition, FDA issues Import Alerts for Detention Without Physical Exam (DWPE) when we have sufficient information to refuse future shipments of a product. The border is one of many integrated checkpoints at which FDA can respond to product problems.

*Rapid Deployment of "For Cause" Inspections.* When FDA has information that raises questions, concerns, or problems, it will rapidly conduct domestic or foreign "for cause" inspections. In such cases, the Agency targets a particular firm or product as an inspection priority based on this information and rapidly deploys an inspection team.

*Expanded Use of Track-and-Trace Technologies.* FDA is working towards the capacity to identify and track a product or group of products along the product life-cycle to facilitate the timely recovery of the violative product and reduce the opportunity for harm. The use of track-and-trace technologies will give FDA the ability to connect the

dots and link important life-cycle information back to the point-of-origin. This will also allow the Agency to communicate targeted and accurate information to the consumer.

*Expanding Laboratory Capacity & Development of Rapid Test Methods.* FDA of the 21st Century must be an agile, scientifically-sophisticated Agency with the ability to develop rapid test methods for pathogens and other contaminants, and ensure that these test methods are available at ports-of-entry to assist in determining whether a product should be admitted into the U.S. To accomplish this objective, FDA relies on its lab capacity to develop and validate methods to increase the number of threats that can be rapidly detected.

*Ramping Up The Cadre of Field & International Staff.* To meet the challenges posed by the increase in the globalization of U.S. drug development, FDA must strengthen its field and international inspection operations significantly. The sheer volume of products, manufacturing plants, distributors, and import sites demands a more robust inspection force. We hope to increase foreign prescription drug inspections (by 50) and sampling in FY 2009; increase domestic inspections and sampling in FY 2009; improve laboratory infrastructures and tools for rapid analysis; and establish and increase FDA's permanent, in-country international presence in China.

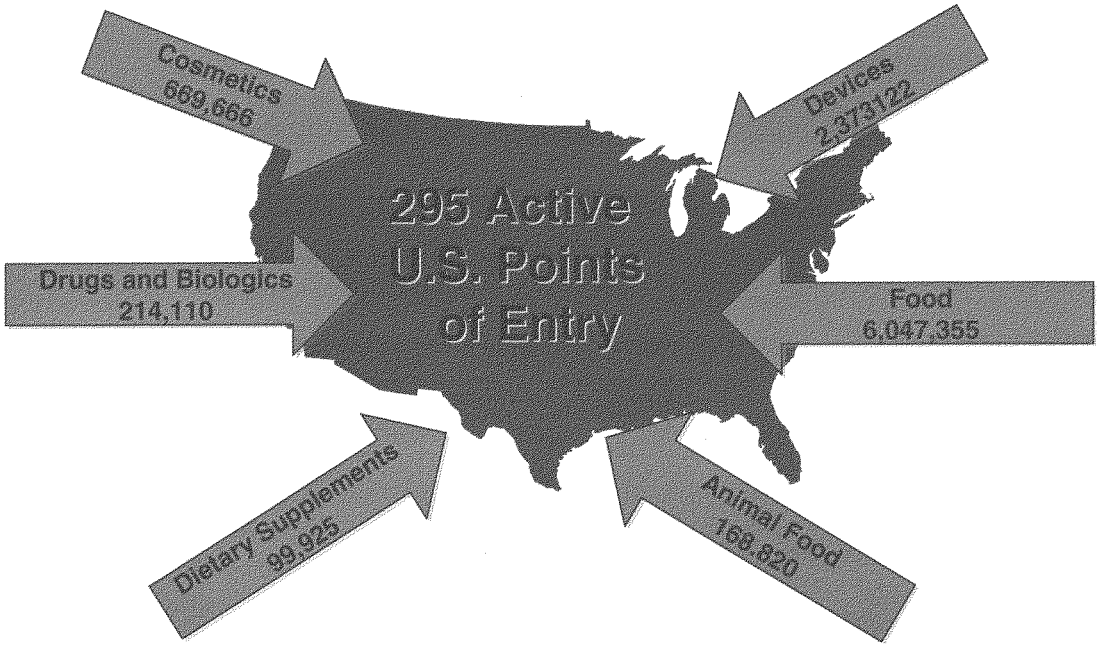
*New Authorities Required.* In addition, FDA is seeking new authorities to help ensure that foreign manufacturers of drug products are in compliance with U.S. law. We recommend statutory authority for FDA to: require certification by third parties, in certain circumstances that imported products meet U.S. importing standards; refuse admission of products for which FDA encounters undue delay, limits, or denials of access to foreign manufacturing sites; expedite destruction of certain unsafe medical products;

and seek asset forfeiture remedies for certain criminal offenses involving fraudulent or counterfeit products.

**CONCLUSION**

I have described for you the tremendous efforts underway at FDA to operationalize a systematic, life-cycle approach to dealing with the globalized system of drug development – a systems-based approach to a systemic problem. FDA is implementing, and will continue to implement, the Action Plan for Import Safety, but this is only a start. The Agency will learn and adapt as we move forward as part of the larger, on-going Agency transformation into an FDA of the 21st century. We need the partnership of Congress to provide the resources and authorities needed for the Agency to enhance our import safety system to handle the multiple and complex changes facing us today. Even with the challenges presented by globalization, the American product supply for drugs and devices continues to be among the safest in the world. We are committed to ensuring that this remains the case. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.

# Volume of FDA Regulated Imports




* Number of entry lines per product category in FY07

# FDA Actions to Improve Safety of Medical Products with Foreign Components

**Subcommittee on Oversight & Investigations**
**Committee on Energy & Commerce**

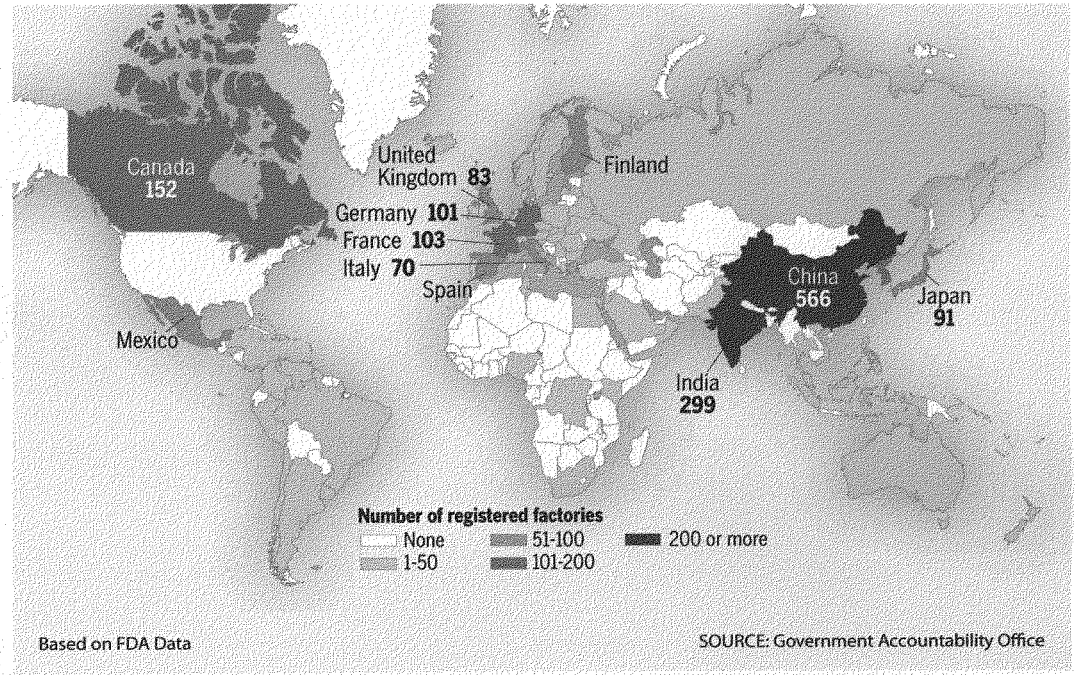
**U.S. House of Representatives**



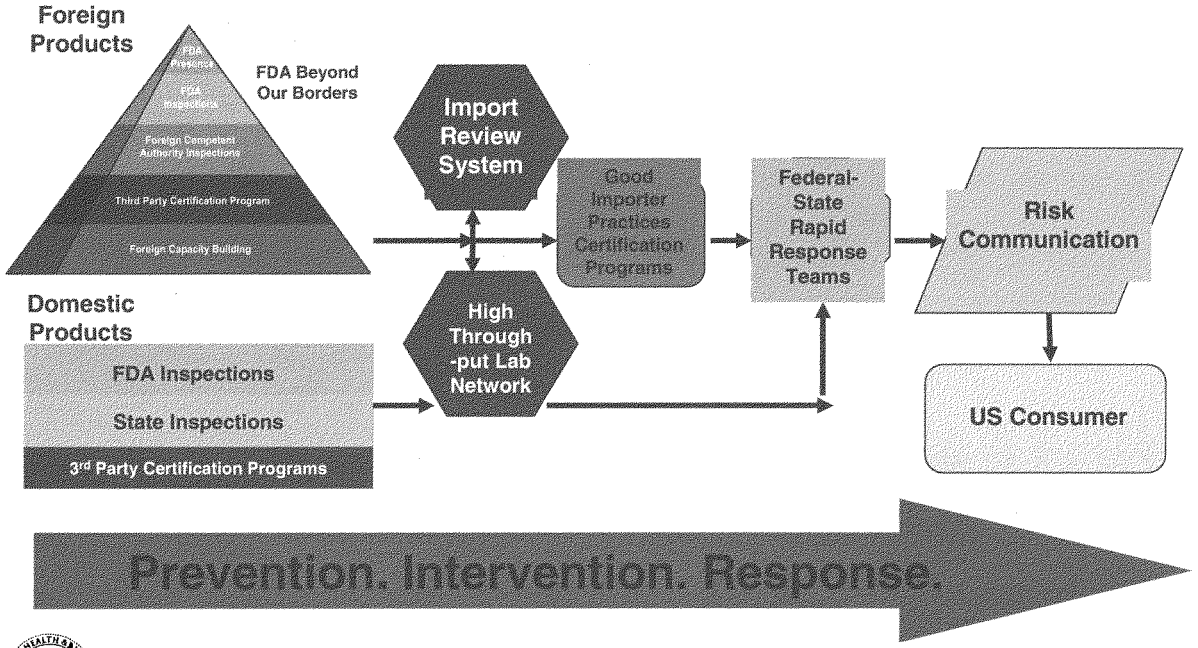
**Andrew C. von Eschenbach, M.D.**
**Commissioner of Food and Drugs**
**U.S. Food and Drug Administration**

**April 22, 2008**

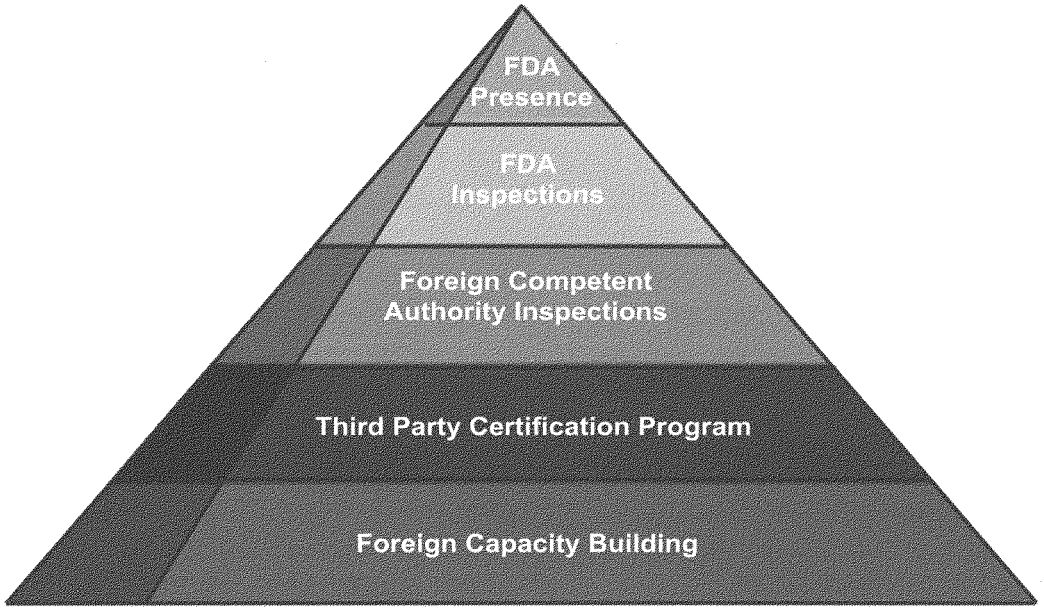
# Making Drugs Far Beyond the Border



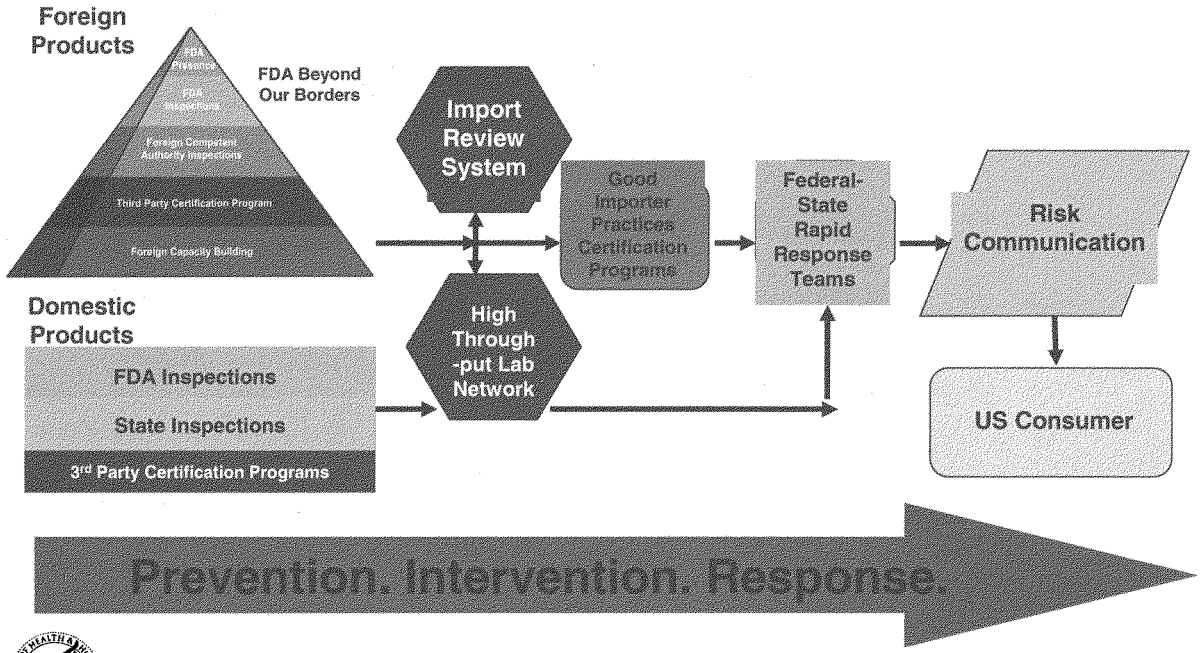
# FDA Oversight of the Product Life-Cycle from Production to Consumption



# FDA Beyond Our Borders



# FDA Oversight of the Product Life-Cycle from Production to Consumption



Mr. STUPAK. Mr. Commissioner, appreciate you being here today, and thank you for taking the time to come to the hearing. We invite you to stick around for our second panel's testimony. The witnesses on our second panel represent more than 100 years of working experience with the FDA in the pharmaceutical industry, as well as significant oversight experience at the GAO. So while we welcome your testimony, we think their testimony would also be valuable in assisting you in making changes at the FDA, and I think it would be worthwhile for you to listen to it.

I'm going to yield my time for questioning at this point in time and turn to the Chairman on the full committee, Mr. Dingell, for questions, please.

Mr. DINGELL. Mr. Chairman, you are most kind and considerate, for which I thank you. Yes or no to these questions, Mr. Commissioner, because I have very little time. Isn't it true that in 2007 there were 3,200 foreign firms registered with FDA to ship drug products into the United States?

Dr. VON ESCHENBACH. I believe that number is correct, sir, yes.

Mr. DINGELL. Now, is it also true that according to a GAO audit, you inspect only about 2- to 300 of those foreign establishments each year?

Dr. VON ESCHENBACH. That's correct, sir.

Mr. DINGELL. At current inspection rates, that it will take FDA more than 13 years to inspect each foreign establishment once?

Dr. VON ESCHENBACH. Yes, sir. And that's why we need a systemic approach.

Mr. DINGELL. Now, GAO estimates that there are 714 drug manufacturing establishments in China registered with FDA; isn't that true? Yes or no.

Dr. VON ESCHENBACH. I believe that to be true, sir. I would have to check that number.

Mr. DINGELL. Now, of these 700 and more firms in China, isn't it also true that you'd inspect an average of 10 or 20 of these each year?

Dr. VON ESCHENBACH. Yes, sir.

Mr. DINGELL. GAO tells this committee the Agency inspects each domestic drug manufacturing firm once every 2.7 years. If FDA is inspecting each foreign firm once every 2 or 3 years, each domestic firm once every 2 or 3 years, how can you justify not inspecting foreign firms at the same rate?

Dr. VON ESCHENBACH. Mr. Chairman, we are completely in agreement that we need to extend our ability to provide regulatory oversight to firms.

Mr. DINGELL. So you're telling me that that situation is indefensible; is that correct?

Dr. VON ESCHENBACH. It is unacceptable for the future, yes, sir.

Mr. DINGELL. OK. Now let us address your budget. GAO reports across 41- to 44,000 for each foreign inspection; is that correct?

Dr. VON ESCHENBACH. I cannot verify that number, sir. We have slightly different numbers, but——

Mr. DINGELL. According to GAO, if FDA were to inspect each foreign establishment once every 2 years, as is required for domestic forms—firms, it would cost FDA approximately $70 million. Have you seen these figures?

Dr. VON ESCHENBACH. Yes, sir, I have.

Mr. DINGELL. Do you agree with them?

Dr. VON ESCHENBACH. That figure may be somewhat higher than our estimates, but it is a reasonable number.

Mr. DINGELL. It is within the ballpark.

Now, to inspect Chinese firms at the same rate FDA inspects U.S. firms, it would then cost FDA about $16 million if we use the estimates of GAO; is that correct?

Dr. VON ESCHENBACH. Approximately; yes, sir.

Mr. DINGELL. Do you differ with those?

Dr. VON ESCHENBACH. Well, Mr. Chairman, I think it is important for me to point out——

Mr. DINGELL. Yes or no.

Dr. VON ESCHENBACH [continuing]. That I believe we need to look not just at the cost of inspections but the entire system that we're using for inspections, and that may require different cost.

Mr. DINGELL. My time here—my time here is much limited, and I do apologize, but I've got—quite frankly, I'm going to be honest with you, I'm establishing that you don't have the resources and you can't do your job.

Now, GAO reveals the most curious finding, in which the FDA has dedicated only $11 million for fiscal year 2008 and $13 million for fiscal year in 2009 to conduct all foreign inspections, and this includes food as well. Are you aware of that finding?

Dr. VON ESCHENBACH. Yes, sir.

Mr. DINGELL. Do you agree with it or disagree with it?

Dr. VON ESCHENBACH. I agree with the finding.

Mr. DINGELL. Pardon?

Dr. VON ESCHENBACH. I agree with the finding.

Mr. DINGELL. All right. In light of these numbers, does the FDA need more resources to conduct inspections of foreign drug manufacturers? Yes or no.

Dr. VON ESCHENBACH. Yes, sir; I've asked for more resources.

Mr. DINGELL. All right. So is it fair for me to say, then, using FDA's estimate—rather, using GAO's estimate of $16 million just for Chinese firms, your resources here under the budget request of $11 million and 13 million are not adequate; isn't that right?

Dr. VON ESCHENBACH. They are not in—they are not in concurrence with GAO's estimates; that's correct.

Mr. DINGELL. OK. Are you telling me that these are adequate or not?

Dr. VON ESCHENBACH. I'm telling you that we are putting those to appropriate use. I have requested additional resources to do more, but I'm trying to make the point that in addition to doing more, we have to do it differently.

Mr. DINGELL. You know, I've been in this business a long time, and I've had Food and Drug Commissioners constantly tell me, oh, we're going to have a new means of doing this and we're going to do this, we're going to be leaner and meaner. It turns out that they are leaner and poorer and weaker and less capable of doing their job. And all these promises that I get from commissioners of Food and Drug about how they are going to do better turn out to be nothing more or less than, quite frankly, hooey.

Dr. VON ESCHENBACH. Mr. Chairman, if you will allow me in the dialogue——

Mr. DINGELL. It is very——

Dr. VON ESCHENBACH. Heparin——

Mr. DINGELL. I've been talking to Food and Drug Commissioners for 40 years. You're not the first fella I've had to skin for not doing his job and coming up here and defending an indefensible situation. So I want to maintain any respect for you, but I can't maintain my respect for you if you keep toe-dancing around the hard facts that curse you with the inability to do your job because you don't have the resources.

Dr. VON ESCHENBACH. Mr. Chairman, I agree with you that we need more resources, but I think the point of the story is, the heparin situation indicated that, even if we had done the inspection, we would not have detected that contamination. That's why I'm trying to make the point to you that in addition to resources for more inspections, which I agree with——

Mr. DINGELL. Well——

Dr. VON ESCHENBACH [continuing]. That we also have to change the system.

Mr. DINGELL. How much—let's come right down to the nut-cutting stage here and let's get a hard answer. How much money do you really need to carry out your responsibilities? In regard to foreign inspection, foreigners are not compelled by absence of inspections by FDA to carry out good manufacturing practices. American manufacturers are. How much money do you need to see to it that you put your treatment of foreign manufacturers of prescription pharmaceuticals and foods in the same position that you put U.S. manufacturers, because you inspect U.S. manufacturers on an adequate level and you do not inspect foreign manufacturers in the same way? How much money do you need to do the job that you have to have? Now, give me an answer to that question.

Dr. VON ESCHENBACH. Well, sir if you took the $45,000 for inspection and multiplied it by the number of facilities——

Mr. DINGELL. Mr. Commissioner, just tell me how much do you need? I'm rather tired of all this toe-dancing. You cannot do your job, you are not doing your job. How much money do you need to do it?

Dr. VON ESCHENBACH. Mr. Chairman, that would require me to present to you a business plan. You gave a figure of $45,000 per inspection, if we were to inspect everything every 2 years——

Mr. DINGELL. How much money do you need to do your job if you do the job on foreigners that you do on Americans? Simple question. I'm sure you——

Dr. VON ESCHENBACH. It would be the number of facilities.

Mr. DINGELL. Repeat it. How much money do you need? You are carrying water for an administration that is not giving you the resources that you need. This committee wants you to have the resources that you need to do the job that you have to do to protect the American people. Sixty-two people died because of bad heparin. Hundreds of others were made sick. You presided over this, because you do not have the resources to do the job that you need to do.

How much money do you need to do the job that you are supposed to do to see to it that Americans are safe? You are the Commissioner of the Food and Drug Administration. You are presiding over an intolerable situation. How much resources do you need?

Dr. VON ESCHENBACH. Mr. Chairman, I would like to have the resources that will enable us to do a systemic overhaul of the entire process, not a figure that's related to the cost per inspection times the number of facilities.

Mr. DINGELL. I don't want—just how much money do you need, on the basis of what I have described is going on, to do the job that you have to do to see to it that good manufacturing practices are conducted in places like China so as to protect the American consumers against unsafe commodities? You have one fine scandal going on, you have others going on with regard to fish and fish products. And you simply are absolutely incapable of addressing your responsibilities.

Dr. VON ESCHENBACH. Well, Mr. Chairman, if you wanted an answer to that question just for drugs, given the formula——

Mr. DINGELL. Well, please answer just for drugs.

Dr. VON ESCHENBACH [continuing]. $45,000. It is $45,000 per inspection times 3,000 facilities, just for drugs. What I am attempting to do is respond to your question.

Mr. DINGELL. I don't want to hear about how you're——

Dr. VON ESCHENBACH. Bigger than that.

Mr. DINGELL. Going to have new methodologies and how you're going to have a new regime for dealing with the Chinese. I just want you to tell me how much it takes you to provide the same necessary inspection for Chinese manufacturers of pharmaceuticals that you have now going on with regard to American manufacturers, so that you can insist that there be good manufacturing practices carried forward in China like they are carried forward in America.

It makes about no sense American manufacturers are getting raw materials in from China that put American citizens at risk. So how much do you need to do your responsibility of inspecting those foreign firms in China to see to it that they carry out their proper responsibilities of giving us good manufacturing practices to assure the safety of the American consuming public? Simple question. How about an answer?

Dr. VON ESCHENBACH. If there are 3,000 facilities in China at $45,000 per inspection, that would be the figure.

Mr. DINGELL. What did he say? What did you say?

Dr. VON ESCHENBACH. If the estimate is that it costs $45,000 per inspection and there are 3,000 facilities, that would be the figure. But I'm trying to discuss with you the fact that I don't believe that is the solution to the problem. I believe it is much more complex and the solution needs to be much more comprehensive than simply inspecting a facility.

Mr. DINGELL. Well, all right. How do you propose to assure, then, that good manufacturing practices are carried forward without inspecting these people?

Dr. VON ESCHENBACH. Well, they need to be inspected. I'm not precluding that——

Mr. DINGELL. All right.

Dr. VON ESCHENBACH [continuing]. This doesn't——

Mr. DINGELL. How are you assured that the facilities are safe? How are you to be assured that they are clean? How are you to be assured that there are not adulterants added? You just have a fine fuss going with the Chinese about whether they are adding illegal components. It is here in the newspaper. Are you aware of this?

Dr. VON ESCHENBACH. One thing, Mr. Chairman——

Mr. DINGELL. Are you aware of this article, Commissioner?

Dr. VON ESCHENBACH. One thing, as I pointed out in my opening statement, is that we cannot do this on an episodic basis of going and coming. We have to have offices that are physically present in these countries where these products are being produced; engaged in an ongoing continuous presence that involves inspections and enhancement of our inspection, at the same time building capacity within those countries.

Mr. DINGELL. See, if I can simplify this and get rid of the toe-dancing here, you've got $45,000 per investigation, you've got 3,000 firms, that comes to $70 million, am I right?

Dr. VON ESCHENBACH. Yes, I will trust your math, sir.

Mr. DINGELL. I note, with apology to you, Mr. Chairman, that my time has expired. I want to get back into these matters at a time later.

Commissioner, I have nothing—no ill will towards you. I have ill will of the most gross sort towards the fact that you come up here and defend a situation that is indefensible, and that you are not soliciting the resources that you need to do your job to protect the American people the way the law says you should, and that you are tolerating an administration which is allowing this kind of situation to obtain, because they are too damn tight to see to it that the American people have the funds that are necessary to protect them against wrongdoing in foreign countries.

I yield back the balance of my time.

Mr. STUPAK. I thank the Chairman.

Mr. Shimkus for questions, please.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Dr. von Eschenbach, it is—we knew it would be an interesting morning, so it is good to have you here. Let me just put this out just to start with. Did you attempt through the budgetary process to solicit additional funds to address some of these funding constraints that the chairman tried to raise?

Dr. VON ESCHENBACH. Yes, sir, I did.

Mr. SHIMKUS. Can you say that again?

Dr. VON ESCHENBACH. Yes, sir. I'm sorry. I did.

Mr. SHIMKUS. Thank you. One of—the success of elected officials, hopefully, is to try to take the complex and make it simple for folks to understand. And I think that is where the frustration comes, because we're not trying to manage an unwieldy bureaucracy. If we had a dime for every outsider who came in to reform the Federal bureaucracy with all the great ideas and then left really being tamed by the bureaucracy, not able to really develop—and there are some people, and we're going to hear it from other panelists later on.

Some of the questions that we pose is, how do we remake the Agency in a new world, in a new era? How do we—some people say

dismantle it. If we were to start over from scratch, what would we do?

I'm not convinced that more money is always the solution. I think there is an argument that—more resources in this case. But, based upon the whole budget and other priorities, as I will address to the other members of the panel, if you have a producer, a manufacturing facility in the United States that has operated 10 years straight, been investigated every 2 years, 5 times, with zero defects, that may call for readjusting priorities and saying, well, you have clearly got this down. We are going to come once every 3 years, and then you can shift to areas that we know need to be inspected.

I like charts and slides, and I can't put this up like you did. But the reality is, you just have a factory, And we have got raw materials coming in, and we produce a product, and it gets to the consumer. And right here in the factory is where everything happens. And in good manufacturing practices, under ISO standards or under any type of thing, they test the raw materials coming in. You test the product that is going out—you should—and you watch the chain inside the factory to make sure there is no contamination and you have—you have a process.

Constitutionally, I know the President proposes a budget. We always get folks to come up here and complain—it doesn't matter what administration—they are cutting one side to give money to another. And we always respond—I always respond what the President proposes and we dispose.

Constitutionally, all spending begins in the House. So, you know, as much as we have identified a resource issue—you have mentioned that you have asked for more resources. It is up to the House of Representatives in our appropriation process, if there is a shortfall, for us to do that. And there may be proposals that come through that will end up doing that. But the military acronym that we used in the infantry, keep it simple. There is another one. There are actually 2 S's, but it is not politically correct to say the second S. Keep it simple.

So based upon the opening statements of your testimony, we have got a resource concern, and we—that—we also know it is a manufacturing evaluation in these factories, and we have technological hurdles that many of us would have hoped we would have been before and seen a little bit more progress than what we think we are at. And so that is kind of the analysis that I have.

We have this chart, the majority put up another one using the country of China and the United States. But it basically has the domestic inspections versus—the inspectors versus the facilities, and there we have foreign, and there is a big gap. The question is, how do we fix that gap? Can you just—and that is the whole premise of this whole hearing, is how do we fix that gap? Tell me how we would do this as simply as possible, because we are all basically simple people up here.

Dr. VON ESCHENBACH. The answer to your very important point of looking at this and arriving at a conclusion is the fact that if we were just simply to increase the number of inspections, which we need to, but that in itself would not solve this problem, that—no

greater example of that than the heparin situation in which inspection would have not detected that contaminant.

And so what I have been attempting to do and what I tried to share with Chairman Dingell is that, in addition to addressing the need to increase our inspections, we also need to overhaul the entire system, everything from the creation of an information technology infrastructure to working with our foreign components and other regulatory agencies in other governments, to working with the private sector in terms of good manufacturing processes and hold them accountable for building quality at the outset.

Mr. SHIMKUS. Because my time is short, get through—I think we'll build on these.

In the second panel, GAO will testify on the next panel that, although the Agency has made positive progress in its databases and in steps to improve foreign inspections, it is not enough, as I said, to close the gap.

And you've already started talking about commenting. We have established in good manufacturing that good manufacturing practice surveillance inspections are critical to assure quality of the drug supply and that more surveillance of foreign firms is needed. And I think you would agree with that. How quickly do you believe it will take us to close this inspection gap, the gap that I just raised in the first question?

Dr. VON ESCHENBACH. I believe that trajectory is going to be limited by our resources and authority and capacity to absorb the change.

Mr. SHIMKUS. So tell us the authority and follow up with the chairman's question on what resources. That's what we need.

Dr. VON ESCHENBACH. The information technology infrastructure could be in by 2010 to 2012 at the very latest. The expansion of the workforce and enhancement of our capacity in our overseas presence could be done again within a matter of 2 to 3 years. So I think the timelines for modernization for the FDA are relatively in a 5-year frame.

Mr. SHIMKUS. We will examine heparin next week more closely. But given the broader implications, would good manufacturing practices surveillance inspection of the SPL plant, which did not occur, have provided information that would have helped in the current investigation? Now, that is a different question than what you have stated before.

Dr. VON ESCHENBACH. Mr. Shimkus, I cannot answer for that question as authoritatively today. I don't believe it would have, based on our current understanding of this investigation and our findings. But it is ongoing. It is an ongoing investigation, and I think the final answer is not yet determined.

Mr. SHIMKUS. Yesterday, FDA released a warning letter on the Chinese-based heparin firm that supply the contaminated product, which said violations cause the heparin to be considered adulterated. If it wasn't for the heparin recall, how long do you think this plant would have shipped adulterated product before it was inspected?

Dr. VON ESCHENBACH. I cannot give you a time on that, sir.

Mr. SHIMKUS. Its U.S. client apparently didn't catch the violations. Wouldn't an earlier FDA surveillance inspection have kept adulterated product off the product?

Dr. VON ESCHENBACH. Well, again, this contaminant was not detectable by the routine analytical methods. So the answer is no.

Mr. SHIMKUS. Well, that's going to be the debating point. It's not detected. But other aspects of a good manufacturing product evaluation might have highlighted flaws in the process where—I concur. I think that under current inspections—see, we're talking about two things, and I had to learn this. One is getting the product after it has been produced, smashing it up, and testing it to see if the efficacy and if it has been adulterated and all those other things. But the whole process of the manufacturing processes is watching as the production line is moving forward. And that is where it is just not testing the end product, it is testing the production of the product.

Dr. VON ESCHENBACH. Correct. There is no question that, based on our inspection, that particular facility would have come under our regulatory intervention and for other reasons, and that in itself, perhaps, would have shut down that particular source. It is my understanding that there are other factories, other sources whose good manufacturing practices were quite appropriate and acceptable, yet the contaminant was still occurring.

So, again, it is the issue of that particular facility had problems. We would have detected those. But that doesn't mean we would have detected this contamination of the heparin supply, because that is much more ubiquitous and would not have been detected by our routine analysis.

Mr. SHIMKUS. Yes. And I'll end on this. Mr. Chairman, thank you for the time.

Our concern is that the possible deviation of the good manufacturing processes, and I—that's where we want to keep these issues and highlight that point.

Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Shimkus.

Mr. Commissioner, on page 4 of the GAO testimony it states—and I quote—"the regular inspections of manufacturing establishments are an essential component in ensuring drug safety," end of quote. Do you agree with that?

Dr. VON ESCHENBACH. Yes, sir, I do.

Mr. STUPAK. Mr. Commissioner, you keep saying that the inspection would not have detected the heparin contamination. You don't know that. You don't know that because you don't know what you would have found if you would have inspected that lab or that plant because you didn't inspect them until after we had these deaths.

In fact, Mr. Commissioner, the opposite can also be true, can it not, that your lack of inspections, like 30 years in China, actually encourages manufacturers to do substitutes like they did in this case here. If I'm not going to be inspected for 30 years, instead of using the pig intestines that you're supposed to use, why not use a sulphate chondroitin? No one is going to catch it, right? So why not use it?

The same thing with melamine. We want to get a higher protein for this industrial food. Why not put melamine in there? They're not going to inspect us. It's going to take 30 years, so you'll never catch us.

So one could easily argue that the lack of inspections actually encourages a less safe product in some of these plants, is that not true?

Dr. VON ESCHENBACH. That is certainly one possibility, sir.

Mr. STUPAK. Sure. So the only definitive answer we can give is, look, we didn't inspect. It is wrong. We are supposed to inspect. We inspect in this country every 2 to 3 years. We must inspect every 2 to 3 years for that deterrent effect that inspections cause, whether it is in the United States or in China or anywhere else in the world, correct?

Dr. VON ESCHENBACH. We need to inspect appropriately. And what I have been trying to express is the fact that we need——

Mr. STUPAK. OK. Before you go there, before you go there——

Dr. VON ESCHENBACH [continuing]. The number of inspections or the frequency but the kind of inspections that we're doing.

Mr. STUPAK. I'm willing to go there with you, but you have to agree with me an inspection is a deterrent.

Dr. VON ESCHENBACH. I'm sorry, sir. I didn't hear.

Mr. STUPAK. Sure. You would agree with me that the inspection is a deterrent?

Dr. VON ESCHENBACH. It can be, yes, sir.

Mr. STUPAK. I mean, in the short time we have been here, toothpaste with the antifreeze, DEG, the cough syrup with the DEG, the melamine, the mixed protein, and now we have the heparin with chondroitin. So inspections actually act as the deterrent.

Now, you want to talk about other ways to do inspections. Our last hearing, I had mentioned in the opening, was January 29th, and you were at that hearing. I know you sat through it, and we appreciated the fact that you did.

And you're talking about setting up—in fact, Kyle, if you can put that pyramid up that the inspector had. He has his FDA on top, FDA presence; and then you have these agreements. You have this pyramid here. It looks at the very top you have the FDA, but on the bottom where the work is being done you're relying on third parties to do it. Is that sort of correct?

Dr. VON ESCHENBACH. No. It is just a little graphic.

Mr. STUPAK. Third-party certification program, foreign competent authority inspections——

Dr. VON ESCHENBACH. That is intended to show that everything channels up to the FDA as the final authority. But, actually, you could turn it the other way around and say the FDA is the foundation for all of that.

Mr. STUPAK. Right. And you were talking—when Mr. Dingell was asking questions, are there other ways to do inspections, you're talking about third parties and having third-party certifications, right?

Dr. VON ESCHENBACH. That's one other addition, yes, sir. It expands our effectiveness and our influence across a wider horizon.

Mr. STUPAK. In one of your earlier slides you show, besides drugs, we have medical devices, animal food, biologics all coming into this country from foreign countries, right?

Dr. VON ESCHENBACH. Yes, sir.

Mr. STUPAK. January 29th, when you were in a hearing, we had a the GAO, and they talked about your third-party inspection programs and—especially on medical device manufacturing. Your third-party inspection program has been around since 2004, and it is called the accredited persons inspection program, the pilot multi-purpose audit program. And it shows that over a 4-year period only 5 inspections had been accredited by these organizations, these third-party organizations. And the GAO concluded that the small number of inspections completed to date by accredited third-party organizations raises questions about the practicality and effectiveness of establishing similar programs that rely on third parties to quickly help FDA fulfill its responsibilities.

So you are saying this proposal you're talking about, even in your testimony, so far at least in medical devices, it is not going to work, it is not effective, there is too few of them. In 4 years, you had 5 inspections only from third parties. So why is this going to be different?

Dr. VON ESCHENBACH. That's correct. And I have spoken to the people in CDRH about what some of those barriers were for acceptance of that third party. There are opportunities, I think, to improve upon that substantially.

The other thing is, of course, what we define by a third party. That could also, of course, be other foreign regulatory agencies which have their own jurisdictions. So it is a much broader scope.

Mr. STUPAK. Sure. But even the FDA says, even in looking at your Beyond the Borders program, the one you talk about in your testimony, we are lacking specific implementation steps. What are the associated time frames would this be on our borders that—there is a lot of talk about this, but it will have little impact to reduce the interval between inspections. The FDA will have to—how do you plan on doing it?

Dr. VON ESCHENBACH. Well——

Mr. STUPAK. I mean, you talk——

Dr. VON ESCHENBACH. First of all, it is a multi-pronged approach. In addition to establishing these FDA Beyond Our Borders initiative——

Mr. STUPAK. OK. What is the main prong? You said this is a multi-pronged approach. What is the main one?

Dr. VON ESCHENBACH. Enhancing our current inspections.

Mr. STUPAK. Enhancing your current inspections. What data are you going to have to enhance current inspections done by?

Dr. VON ESCHENBACH. We did more foreign inspections this year than in the history of the FDA. We can do even more next year in targeting——

Mr. STUPAK. Even with $13 million and each one costs $45,000, you're going to do more?

Dr. VON ESCHENBACH. We are targeting 500 foreign inspections next year in addition to creating a foreign presence.

Mr. STUPAK. Five hundred at $45,000. I wasn't a math major. That would be about $200 million you're going to need, and you ask for $11 million. How is that going to jive?

Dr. VON ESCHENBACH. There is already an inherent—it is up to 500. We are up to 350, approximately.

Mr. STUPAK. OK. So I wasn't a math major. That would be $20 million, not $200 million. So, either way, $20 million is about half of what you have asked for. So how do you get there?

Dr. VON ESCHENBACH. Well, there is also the capability of leveraging what we already had in play.

Mr. STUPAK. Leveraging with who? Who is going to do the inspections if you're not doing them? How are you leveraging? Who is doing them?

Dr. VON ESCHENBACH. We have inspectors in the Agency——

Mr. STUPAK. Sure.

Dr. VON ESCHENBACH [continuing]. And we'll need to detail them to the foreign inspections that we are targeting.

Mr. STUPAK. I see. So——

Dr. VON ESCHENBACH. One of the things that is more efficient——

Mr. STUPAK. Your IT system is broken. You don't—how are you going to prioritize it? The GAO says you can't even tell us what is being produced and sent to the United States. Therefore, it is hard to prioritize what is most significant to prioritize your inspections. So once you start with your IT system so you know who is out there, what are they sending? What is the right of the American people?

Dr. VON ESCHENBACH. Yes, sir. And we started that 2 years ago. That's in midcourse. We anticipate——

Mr. STUPAK. When will it be done, your midcourse?

Dr. VON ESCHENBACH. Pardon me?

Mr. STUPAK. Your midcourse, when will it be done? Two more years?

Dr. VON ESCHENBACH. Two more years.

Mr. STUPAK. So 2 more years before we have an IT system that can tell us what is out there, who is producing what, and then be able to prioritize our inspection. So we have got to wait 2 more years before we can even prioritize?

Dr. VON ESCHENBACH. It is incremental. It is improving consistently and constantly, but it won't be at full maturation until 2 years. The data center, for example, at White Oak at our consolidated facility is expected to open up in early '09.

Mr. STUPAK. Early '09.

OK, it is my understanding that you proposed but not yet implemented a Foreign Vendor Registration Verification Program. When is that program going to start? I understand it is supposed to help improve the accuracy of the information in your databases. And the way I understand the program, your Foreign Vendor Registration Verification Program, the FDA is going to contract with an external organization to physically conduct site verification on the registration data of the firms shipping drugs and other FDA-regulated products of the United States. When is that going to start? Have you began the Foreign Vendor Registration Verification Program?

It sounds to me like you're saying we can't do it internally, so let's get someone externally to do it. Have you begun that process?

Dr. VON ESCHENBACH. No. It is a matter of leveraging where those verifications are occurring for multiple purposes. We can benefit from that. Because, as you pointed out in the data system, there is a lot of redundancy. There are, in fact, firms that registered and are no longer shipping to the United States, and that is what created that discrepancy in the database.

Mr. STUPAK. Right. So you're going to have this Foreign Vendor Registration Verification Program. When is that going to start? Have you contracted with anyone to do this? That's what I'm asking.

Dr. VON ESCHENBACH. That is in process, And I cannot tell you when that will be fully implemented. But it is in process.

Mr. STUPAK. '09?

Dr. VON ESCHENBACH. I would have to get back to you about that, sir.

Mr. STUPAK. Do you have any money in the budget to implement a Foreign Vendor Registration Verification Program?

Dr. VON ESCHENBACH. These are parts of the planning of the budget, yes.

Mr. STUPAK. But do you have in '09—is there a line in there for a Foreign Vendor Registration Verification Program?

Dr. VON ESCHENBACH. I cannot specifically speak to a line item for that.

Mr. STUPAK. OK. Shouldn't we really assign, in fact, some of the legislative proposals have indicated a unique identification number to every foreign establishment that makes a drug and that have all databases, including those used by FDA, Customs, track activities such as inspection, products alert? Shouldn't we have that?

Dr. VON ESCHENBACH. Yes, sir.

Mr. STUPAK. Do you have that program ready to be implemented where every establishment——

Dr. VON ESCHENBACH. That is being done in collaboration with the other agencies that you have talked about.

Mr. STUPAK. But you can't give them a foreign inspection number until you know what firms are out there, right? You have got to establish the firms first before you can give them a foreign inspection number, right?

Dr. VON ESCHENBACH. Correct.

Mr. STUPAK. OK. So it sounds like you're verifying what is out there first, correct?

Dr. VON ESCHENBACH. Well, it is a combination of both. It is through registration and our verification.

Mr. STUPAK. OK. My time has expired. Mr. Burgess for questions.

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. von Eschenbach, welcome again to our humble little subcommittee. Since most of the reason for this hearing today, at least in my opinion, revolves around the heparin story coming out of China, let's stay on that for just a minute. What is the culprit there that is making people sick?

Dr. VON ESCHENBACH. It was a compound that was added to the heparin that you alluded to earlier, the hypersulfated chondroitin sulfate.

Mr. BURGESS. When you say "added," did Baxter add this?

Dr. VON ESCHENBACH. No, sir. This appears to be coming from the source in China.

Mr. BURGESS. Well, of course, the counter from—at least my understanding from reading the papers today, the Chinese say, well, it may have been added in the United States. So we have a fair degree of certitude that that contaminant was in the product before it was ever imported to this country?

Dr. VON ESCHENBACH. Yes, sir.

Mr. BURGESS. Well, how would someone get it in there?

Dr. VON ESCHENBACH. We haven't determined that at this point, sir.

Mr. BURGESS. We're reasonably sure that this hypersulfated chondroitin sulfate is the culprit?

Dr. VON ESCHENBACH. Yes, sir.

Mr. BURGESS. What are the tests used to detect that?

Dr. VON ESCHENBACH. Well, upon noticing the adverse events and searching for what the offending component was within the heparin the patients were receiving, the routine analytical methods did not detect any abnormality. It wasn't until we did very sophisticated testing with nuclear magnetic resonance and a variety of other very sophisticated strategies in highly specialized laboratories that we were able to detect the presence of something that shouldn't have been there. And then that was subsequently identified as this particular compound.

Mr. BURGESS. Now, did the Food and Drug Administration decide to start doing the nuclear magnetic resonance testing on the compound?

Dr. VON ESCHENBACH. Yes, sir. We launched that investigation. We engaged both within the FDA as well as outside the FDA the appropriate scientists. And then, once we identified the compound, we actually developed an assay that could be used for routine screening to be able to find that contaminant in heparin; and that was distributed essentially worldwide so that many agencies around the world are now using our assay and evaluating their own heparin supplies.

Mr. BURGESS. But in December of 2007, no one, including the FDA or any of the manufacturers—or the importers, rather, or any other country would have been using that test?

Dr. VON ESCHENBACH. No, sir. It didn't exist.

Mr. BURGESS. It didn't exist. So it would have been impossible, even had you—we have heard all the stories about perhaps the wrong manufacturing location was selected for inspection. But even had all of the inspections—even if we had had an inspector at every plant in every foreign country, likely as not this contaminant could have found its way through?

Dr. VON ESCHENBACH. Yes, sir.

Mr. BURGESS. In fact, it seems very likely that this contaminant would have found its way through.

Mr. Stupak brings up a good point about we have got the melamine in the dog food and now we have got hypersulfated

chondroitin sulfate in the heparin. And you do have to wonder, is this just a very unscrupulous merchant with its thumb on the scale or is someone actively trying to do us harm? And, obviously, I wouldn't ask you to speculate since I'm doing that for you, but it does raise those very big questions.

So what ability do we have—now, we—I realize the dog food wasn't your purview. But what ability do we have to anticipate the next level of larceny or terrorism—if I can use that word—that might come our way in our food or the active pharmaceutical ingredients that are coming from overseas?

Dr. VON ESCHENBACH. Well, our ability to protect and promote the public health is going to be dependent upon the information that we have to act upon. And what I am suggesting in this system's approach to our ability to now deal with products that are coming from all over the world, have an extraordinarily diverse complexity, that we have to be able to be much more present at the source of the production of those products.

Mr. BURGESS. Not only that, you have got to think like a thug and have the same type of simulations and—you could not intuitively have known that this product was going to enter the pipeline. I mean, none of us——

Dr. VON ESCHENBACH. No.

Mr. BURGESS [continuing]. Fat, dumb, and happy last Christmas would have had any idea that this was about to happen to our pharmaceutical industry.

I guess what I'm asking is, is there a room of guys over—or men and women over at the FDA, one of whom who thinks like criminals, one of whom thinks like terrorists, and they try to run these simulations? Where is our new vulnerability——

Dr. VON ESCHENBACH. And, in fact—in fact, that has been a model that we've benefited from as we looked at our food protection plan. Because we had been approaching food from the perspective of food defense as it related to intentional contamination, as well as food safety as it related to the unintentional contamination that could come from bacteria, et cetera, and chemicals; and we appreciated the opportunity to integrate that into a cohesive system that is based on important intelligence as well as modern scientific analytical tools. And that's a concept that we have extended to all of the products that we regulate, and it is inherent in this prevention/intervention response strategy.

Mr. BURGESS. One of the things that really was striking when we had our food safety hearings earlier this year was the fact that there is no communication between the various commercial interests that are overseas importing food back to our country. There was no communication between them if they had a bad supplier or they got something that was contaminated within their shop, that they didn't communicate I guess largely because of competitive concerns with their counterparts.

But really even more disturbing is that they wouldn't communicate with the Food and Drug Administration; and it just seems like now, with the melamine in the dog food and the hypersulfated chondroitin sulfate in heparin, that there are some minds out there that require that we be so vigilant that we are willing to give up some competitive influence or, if nothing else, the Food and Drug

Administration may need to require that people be forthcoming with this information lest we get a bucket of chicken wings full of polonium over here someday, which none of us would like to see.

Dr. VON ESCHENBACH. And to that point, Dr. Burgess, we have consistently enhanced our dialogue in collaboration with other Federal agencies, importantly, our relationship with Homeland Security.

Mr. BURGESS. Now, earlier—well, actually, I guess it was last year—I introduced H.R. 3967. Mr. Hubbard helped us a great deal with that. And the whole idea there was to have the ability to stop something from coming into the country if we knew it was wrong, if we knew it was bad. Right now, it doesn't seem like we have the tools at our disposal, and Ranking Member Barton mentioned that in his opening statement, that we don't have a way to stop this stuff from coming in. And that is—going forward, that just seems to me to be something that is so critical that we need to incorporate that into whatever plan you come up with or we come up with.

The whole concept of equivalence came up when we talked about food safety, the equivalence standard that the United States Department of Agriculture has for about 20 percent of the jurisdiction that it has over imported food; and the Food and Drug Administration has an 80 percent jurisdiction over imported food but doesn't have that same equivalency standard that, even though the manufacturing is in a different country, it has got to be equivalent to what the manufacturing process would be in this country. And it is my understanding we don't even have that equivalence standing for the production of active pharmaceutical ingredients.

Dr. VON ESCHENBACH. One of the points of FDA Beyond Our Borders is to work effectively with our foreign counterparts so that these products meet our standards before they are able to come into this country. And there is a dialogue in—that I think we need to find for harmonization.

I convened the first meeting of all of the international regulators from mature regulatory agencies around the world, all 27 of them—24, I believe—that came to the meeting 2 years ago to begin this dialogue, and we've had 3 meetings since.

Mr. BURGESS. Well—but it seems like the standards already set by the USDA would be—again, that equivalency standard would be one that would be pretty easy. We talk about harmonization. That is great. But we have a standard out there that works reasonably well for the 20 percent jurisdiction that is out there. And at least for the active pharmaceutical ingredients, it seems like that is something that we should be quick to pick up.

Dr. VON ESCHENBACH. There may be some issues with regard to the individual products that may or may not create unique concerns about equivalence, but it is an area we are discussing.

Mr. BURGESS. Do you have—does this discussion we are having about heparin right now—and I realize that heparin would not fall into the debate about bio-similars or bio-identicals. But just the fact that we have got the story out there with an adulterated product, does this affect the debate on the so-called generic biologics—bio-similar products that this committee—Health Subcommittee of this full committee is investigating?

Dr. VON ESCHENBACH. Well, again, I think, Dr. Burgess, it reflects the important testimony that you heard from our scientific advisory board at a previous hearing and that one other component of this systematic modernization of the FDA is that we have a really robust and strong scientific infrastructure that will give us the modern tools of science and technology to make discriminating decisions about these complex and very difficult products to understand but to do that in a way that gives us greater insight from a scientific perspective about those products. And I think whether it is the—dealing with the complexities of bio-equivalence or understanding the components of a drug that is causing an adverse reaction, building the scientific infrastructure is one other pillar to this new FDA.

Mr. BURGESS. Let me just ask you one other question quickly, because it is about money, and Chairman Dingell went to some lengths to talk about money. We have heard about the administration's budget. Of course, Congress has—April 15th has come and gone, and we have not passed a unified budget resolution. Clearly, it is up to the House. It is up to House leadership. In fact, it is up to the Speaker of the House to work—initiate the work on those appropriations bills, those critical appropriations bills that you're going to depend upon to get your funding.

The stories that I'm hearing are likely that we will not be able to do that work this year. The environment is just too toxic and too contentious. As a consequence, there will be a continuing resolution at the end of the fiscal year, which essentially will leave you at level funding.

So although it is great to go into some sound and fury about budget numbers, the reality is, the reality for your agency, is what is being handed to you by the Speaker of the House is you're likely to have level funding this next year, this next fiscal year; and how is that going to impact your ability to do all of these things that we have talked about this morning?

Dr. VON ESCHENBACH. Well, I believe it has been my responsibility in the 2½ years I have been at the FDA to critically assess the status of the Agency, to bring multiple partners together to begin to define a strategic plan for what the Agency needed to accomplish and how it needed to change and what those initiatives would be that would require support, would require resources, would require new authorities, and we have done that across the wide spectrum. Everything from our food protection plan to now addressing issues——

Mr. BURGESS. But in order for you to do our job and for us to do our job—and, unfortunately, right now, that does not seem to be the case.

I will yield back the balance of my time.

Mr. SHIMKUS. You have no time to yield back.

Mr. STUPAK. Mr. Melancon for questions, please.

Mr. MELANCON. Thank you, Mr. Chairman.

In listening to Mr. Burgess—and we're talking about the level funding and trying to blame the Speaker, I think we can go back about a couple of years and blame the previous Speaker and the majority. So if you want to put blame where it stands looking at GAO, this decline started sometime back if I recall.

Not trying to put any blame on anybody, but the article today in the New York Times, one of the things that catches my attention is Chinese imports—you've had exported poisonous toothpaste, lead-painted toys, toxic pet food, tainted fish, and now contaminated medicine. It seems to be getting worse rather than better. I mean, with all this that is surrounding us, did you not expect that maybe we would be talking about heparin or some other medication that is coming from China today?

Dr. VON ESCHENBACH. I believe what has occurred is not necessarily things are getting worse. I think what we have done is systematically uncover what has been a significant set of issues, and we're addressing them systematically in an effort to resolve them. I believe even—if you'll give me a moment—when we first encountered the problem with melamine in pet food, our ability to interact and work with our Chinese counterparts at that time was nowhere near as effective as this most recent episode with heparin, where we had immediate and rapid access into the country. We worked directly with our counterparts at the SFDA, sharing specimens, engaging in analytical processes. So I believe we're making progress, but the problems are substantial, and they require substantial effort.

Mr. MELANCON. Well—and I hear what you are saying. But then when you suggest that the heparin was contaminated in China, the Chinese are saying it got contaminated over on our side. Isn't there some memorandum of understanding or agreement that is supposed to be going on between the two countries or is this just pointing the fingers at each other?

Dr. VON ESCHENBACH. No. There was a scientific dispute, if you will, about an analytical methodology; and we're engaged in the discussion of that. We believe the analytical methodologies that we have applied and are being applied by others are the correct ones.

Mr. MELANCON. Well, it appears to me that this memorandum of agreement is more like a memorandum of let's disagree. And it is just—it is a growing tension, I think, between the two countries. You know, I think what I read in the article, that there was less pointing of fingers between the Germans and the Chinese than between the United States and the Chinese over this heparin issue.

Given China's fundamental difference and understanding of science used to assess what is causing the tainted heparin problem, can we trust the Chinese to adequately regulate our drug supply, since it appears that FDA isn't willing to do it?

Dr. VON ESCHENBACH. Well, the FDA is working very directly with our counterparts in China. They are engaged, I think, in a very conscientious effort to improve their entire system within the country. I have met with their Minister of Health who believes this is as important to the health and welfare of the Chinese people as it is to the rest of the world.

Mr. MELANCON. What is it that they have done that you can document?

Dr. VON ESCHENBACH. Well, as part of the memorandum of understanding, we have really engaged, as I just pointed out with the heparin situation, in an opportunity for us to work directly with them, specimen sharing and the ability to get to the bottom of product——

Mr. MELANCON. That's why I concern myself with this memorandum of misunderstanding or disagreement in that they are immediately saying it is your fault, it isn't our fault. I mean, do we not work through the process of how the science is going to be done on these products so that we'll know?

Dr. VON ESCHENBACH. Yes, sir. We convened an international meeting at which they were present, and the scientists internationally have been engaged in this discussion, and we are continuing that.

Mr. MELANCON. Let me go back to the—when we started. GAO is showing that, in the beginning of '02, we started a decline in inspectors. Do you have any numbers that go back past '02 that shows that—the budgetary and the number of inspections or inspections that were done overseas as opposed to inspections that are done here? I'm trying to see if there was a trend or if this just started at a certain period of time and is it all budgetary.

Dr. VON ESCHENBACH. I cannot give you specific numbers. My recollection of what I evaluated when I looked at this, coming to FDA, was that the number of foreign inspections had remained relatively flat, while the number of products and firms that were producing things and coming into the United States was growing almost exponentially. So the gap was substantially widening. And we obviously need to keep pace. So the—I don't know that the inspections went down as much as stayed flat, while the demand substantially increased.

Mr. MELANCON. So as we've exported all our manufacturing to other countries we have not kept up with the overseeing of the manufacturing of these products?

Dr. VON ESCHENBACH. That's correct. We've not kept up with the globalization that has occurred in the marketplace.

Mr. MELANCON. And we're outsourcing again. Maybe we can outsource people to go out there and do them.

I've had some conversations with some company representatives. They seem to be opposed to any form of charge by the Department to pay for the inspections, and I understand that they don't want to have any cost—any additional cost incurred. How do we pay for this since we don't have the money, since we are left with a huge deficit and a huge problem?

Dr. VON ESCHENBACH. I'm sorry.

Mr. MELANCON. It's OK.

Dr. VON ESCHENBACH. Well, I have, again, consistently proposed that the FDA need—should and is on a broad base as far as its resource infrastructure. Budget appropriations are an important part of that. User fees have also been a part of our budget when applied appropriately and segregated appropriately so that they're not influencing our regulatory decisions. And I think user fees are an alternative mechanism of support.

Mr. MELANCON. Did someone in the Department, you or someone within the Department that can make decisions, surely saw this problem coming toward us, did they not?

Dr. VON ESCHENBACH. I'm sorry, sir.

Mr. MELANCON. The inspection problem or the ability to not inspect, to have the manpower to have the money, no one saw this coming? Did we just wake up last month and say——

Dr. VON ESCHENBACH. No, sir. When I arrived at FDA 2½ years ago, I set 5 strategic priorities, one of which was globalization. And that was an effort to recognize what was occurring and what had been pointed out by others and to really begin a very aggressive, systematic, and systemic approach to being able to address the complexity and the magnitude of the problem. And what we have been discussing are the parts and pieces of that.

Mr. MELANCON. Well, the difficulty I have with an aggressive approach is that 2½, 3½ years later we are here; and we are getting dumped on with chemicals and bad drugs and such as that. Did you come to the Congress? Did you go to the White House? Did you say to somebody, look, we need to have the money. Either give it to us in user fees, inspection fees or set up a mechanism where the companies can send people over there to inspect the products that are going to be part of their final products? Did we do any of that?

Dr. VON ESCHENBACH. Yes, sir. For the period of time I have been at the FDA, I have consistently and continuously requested increases in the budget. That trajectory is continuing. I have consistently attempted to bring forward plans of initiatives that I believed would be demonstrated to have impact and for which we could be held accountable for outcomes. We have talked on multiple occasions, just even this morning, about the transformation of our IT infrastructure.

Mr. MELANCON. So you requested the White House for the increase of the budget over the periods of years?

Dr. VON ESCHENBACH. Yes, sir.

Mr. MELANCON. And they have rejected that. How much more did you ask for for the inspectors from the White House?

Dr. VON ESCHENBACH. While I was going through the budget presentations and made my request to the Department, that subsequently went on to the administration and then recommended to the Congress.

Mr. MELANCON. How much? What was the dollar amounts that you asked for to make sure that we were adequately supervising overseas manufacturing of our products?

Dr. VON ESCHENBACH. Well, I asked for additional resources; and I cannot give you that specific number today.

Mr. MELANCON. If you could get that back to us so that we could have that as part of the record, I would sure appreciate that.

In this changing world that everybody has been talking about for the last 10 years, surely people have looked to the future of where the jobs are going to go, or maybe they didn't look to where the jobs are going to go and where the manufacturing was going to be done. If we were friends with everybody in the world, I probably wouldn't be sitting here having this conversation. But, as Mr. Burgess contemplated, there are some people that don't really like us, and this may be an avenue for them, through terrorism, to come after us, and that is the last thing we need. And so, I would wish that you would impose upon the administration the importance of food safety to this country's security.

I think my time is out. I yield back my time, if I have any.

Mr. STUPAK. I thank the gentleman.

Mr. Green for questions, please.

Mr. GREEN. Thank you, Mr. Chairman.

I would like to welcome Dr. von Eschenbach back.

Mr. Chairman, I apologize for not being here for opening statements. I ask unanimous consent to have my full statement placed into the record. I just want my full statement——

Mr. STUPAK. Without objection.

[The prepared statement of Mr. Green follows:]

STATEMENT OF HON. GENE GREEN

Mr. Chairman, thank you for holding this hearing today on the FDA's foreign drug inspection program. I think this a very important topic.

As we know from previous hearings in this subcommittee and the FDA's self assessment report, "Science and Mission At Risk," the Agency is underfunded and does not have enough employees or resources to protect the country against unsafe drugs, medical devices and food.

The inadequacies of the FDA's foreign drug inspection program were most recently highlighted with the blood thinning drug heparin.

Initially, the tainted heparin was believed to be an isolated incident and the active ingredient in the drug was traced back to a Chinese facility that had never been inspected due to confusion in the FDA because the name of the facility was confused with another plant with a similar name.

However, further investigations found the contaminated heparin products have been found in at least 10 countries, not including the United States, and have been linked back to 12 different Chinese companies that were somehow involved in the tainted heparin. A man-made chemical is believed to be responsible for the adverse reactions and 81 deaths associated with the drug.

We should not be surprised by the lack of inspections in foreign drug establishments by the FDA.

According to the GAO in FY07, there were 714 drug establishments in China, but only 13 inspections were conducted over the entire year. As another example, India had 410 drug establishments and only 65 inspections were conducted.

What is alarming is the fact that eighty percent of the active pharmaceutical ingredients of drugs consumed in the United States are manufactured abroad and most of those drugs are manufactured in China and India. And, the FDA has publicly acknowledged that some foreign facilities may never be inspected.

Clearly, 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.

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

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Mr. GREEN. Mr. Chairman, this is not necessarily a question for our FDA Commissioner, but I find it ironic, because in our full committee and even our Health Subcommittee over the last few years, particularly after the 2003 Medicare Prescription Act or even before, we have had a number of hearings by our committee concerned about my constituents going on the Internet and importing pharmaceuticals, whether it be from Canada or Europe or whatever, because they don't really know where they come from. And the argument we heard many times is that we don't know where they come from. We don't know if you're ordering it from a Canadian pharmacy, or you are maybe ordering it from a China pharmacy, or somewhere else.

And yet now it seems like what we're hearing is our drugs that are approved, that 80 percent of the ingredients are imported. And,

you know, we have learned that there is no oversight over that, or I guess very little, if any.

I guess my concern, if I was in the business of producing a pharmaceutical, just like if I was in the business of producing any other product, the responsibility for that assures the oversight with the FDA but also with that person or that company who is importing that ingredient, whether it is active or inactive, is part of something we are putting in our body that is a pharmaceutical.

Has there been any discussion on what the pharmaceutical companies—I know our next panel will hear that. Has the FDA looked and said, OK, did you all go to this plant in China to look for these ingredients? What—let me see your track record of what you did. Because you are importing that product to put it in something that you're putting your name on.

Dr. VON ESCHENBACH. You make a very, very important point, Mr. Green, that the corporate responsibility is an integral part of this whole effort and the safety; and FDA holding them accountable for that has been a part of this. It is required that they carry out their own quality assurance and are vigilant in the screening of their materials, and so I do concur with you that that is an important part of the effort, and FDA holds them accountable and that secures our supply of drugs.

Mr. GREEN. Is there any information you can give the Oversight Committee, for example, on heparin or whatever else that may come along? When this developed, did the FDA go to that company and say, OK, let's see what you did on the quality of this product that you're selling to our constituents?

Dr. VON ESCHENBACH. Right. When a company imports an ingredient to—an active pharmaceutical ingredient to incorporate in the development of a finished product, they are responsible and accountable for assuring the quality of that product, and they have to assess it and test it. I think the point we were making earlier is, with regard to the contaminant in heparin, none of the conventional tests could detect that contaminant. So it was something that was beyond our ability to recognize using conventional testing.

Mr. GREEN. And I think what you are going to hear from most of us is that the FDA is the traffic cop, and you need more resources to do that. And I appreciate you asking the administration.

It is also our job as Members of Congress. Although when the Chairman miscalculated $200 million to $20 million—that's why we are not the Appropriations Committee. But if we were, we would probably be—what we've heard for a number of months—we would probably be saying, yes, we need to upgrade and provide a lot more funding so you can do your job as the traffic cop but not take away the corporate responsibility.

Because I am speeding down the road, and I have an accident, sure, if there had been a policeman there to stop me, I wouldn't have had that accident, but it is still my responsibility for speeding down that road. And, Mr. Chairman, I think that's what we need. Maybe the next panel will explain the corporate responsibility along with our effort to try and make sure the FDA does their job as a traffic cop.

I yield back.

Mr. STUPAK. Thank you.

Mr. Barton for questions, please.

Mr. BARTON. Thank you, Mr. Chairman.

Dr. von Eschenbach, my understanding is that recently the FDA has announced some of its preliminary results in the heparin investigation, and it is my understanding that your agency has indicated that you have traced the contaminated material to China. Is that right?

Dr. VON ESCHENBACH. Yes, sir, that's correct.

Mr. BARTON. OK. Now it is also my understanding that the Chinese authorities don't accept the FDA's findings. Is that correct?

Dr. VON ESCHENBACH. It is my understanding that the one difference is that they believed that there was product with which there were adverse events associated, but they could not find the contaminant in that product and, therefore, they were refuting the causal link. Our assay, our methodologies, which are much more sensitive, did in fact find the contaminant in that product. So that's where there is a very specific difference——

Mr. BARTON. Where do we go from here?

Dr. VON ESCHENBACH. Well, I think what—where we are at this point is we have assured that the supply of heparin in this country today is safe. We have prevented any further import of product coming from China from—through an import alert, from companies that are in question. And everything that is coming is being tested before it is allowed into the United States to be sure it is free of the impurities.

Mr. BARTON. So you—under current law, the FDA has the authority in this case to prevent any product manufactured in China of that name from coming into the country? So even if the Chinese don't agree, it really doesn't matter, because the FDA can say you can't bring it in?

Dr. VON ESCHENBACH. That's correct. We deemed it adulterated.

Mr. BARTON. OK. Now, do we—my understanding is that you and Secretary Levitt have indicated that you do think that the FDA needs explicit authority in terms of foreign imports and foreign inspections to categorically prohibit certain products when you have found defects in them. Is that correct?

Dr. VON ESCHENBACH. What we've requested, Mr. Chairman, if I can be explicit, is we can deny a product entry into this country if we deem it adulterated. What we'd like to do is extend that to not allowing a product to come in if we haven't had the opportunity or been given the opportunity to inspect facilities from which that is coming. So the very fact we have been denied access to the facility in itself would allow us——

Mr. BARTON. So you've got the authority under existing law to prohibit adulterated material. What you want is the authority to say, if they refuse to allow U.S. FDA inspectors, then you can also prohibit the material?

Dr. VON ESCHENBACH. Exactly. Yes, sir.

Mr. BARTON. Now, when Chairman Dingell—I wasn't here, but when Chairman Dingell was asking questions, my understanding is that he wanted you to give some assurances in terms of numbers of increased inspectors and in numbers of increased dollars and assets that you would need in the FDA to instigate these overseas in-

spections. Now you told me in my office that you want to locate FDA inspectors permanently overseas, is that correct?

Dr. VON ESCHENBACH. Yes, sir, that is correct.

Mr. BARTON. All right. Do you have an estimate yet as to how many inspectors and how much additional resources in terms of dollars that you would need to implement this kind of general plan that you have talked to me about?

Dr. VON ESCHENBACH. With specific reference to the first initiative in China, we would anticipate placing 13 FDA personnel. Eight of them would be FDA coming from the United States, and five would be local residents that we would employ. The approximate cost of that—that would also include our presence in Beijing, Guangzhou, where there is major food production, and Shanghai, where the largest exports are occurring, and the approximate cost of that operation is about $13 million.

Mr. BARTON. $13 million. Now, in that specific case, have the Chinese authorities been in consultation with you and your staff?

Dr. VON ESCHENBACH. I apologize, Mr. Chairman. May I correct that? It is 13 people, but $3.1 million. I apologize.

Mr. BARTON. That is a better number. So long as it is an adequate number. Have you or your staff consulted with the Chinese authorities about this specific case?

Dr. VON ESCHENBACH. Yes, sir.

Mr. BARTON. If so, are they supportive, neutral, in opposition to it?

Dr. VON ESCHENBACH. They have been very supportive across a number of their ministries, but we are awaiting approval from their foreign office. That is still outstanding. But in our interactions with counterparts and their regulatory agencies, as well as their export agency, AQSIQ, and the Ministry of Health, they recognize this is an important opportunity to enhance capacity.

Mr. BARTON. Now, if this plan materializes, will the inspectors in China have the same authorities as the inspectors in the United States? In other words, can they go into any facility at any time or do they have to go through some procedure that would make it possible to let there be a cover-up before they were able to actually undertake the inspection?

Dr. VON ESCHENBACH. No, we will anticipate they would have the same authority as if they were coming from the United States.

Mr. BARTON. OK. On a slightly different topic, it has been suggested that inspections overseas, facilities overseas that the U.S. FDA does inspect, that they be inspected on the same timetable as domestic facilities, i.e., at least once every 2 years. Our GAO friends are going to testify later today that if we implemented that system, it would cost at least $70 million a year just for China—no, $70 million a year in total, and of that cost $17 million would be in China by itself. One, do you agree with those numbers? And, two, if you do agree with those numbers, is this funding level something that the FDA can digest without too much of a growing pain?

Dr. VON ESCHENBACH. Well, to be clear, I don't disagree with the numbers per se. What I have tried to explain to Chairman Dingell was I really think the conversation has to be broadened beyond just the number of inspections and their frequency. I believe that it needs to be a tiered approach. There are some facilities that,

quite candidly, need to be inspected more frequently and more intensively than that and others, by the very nature of their product and their history on a risk-based approach, may very well be able to be inspected less frequently than that with oversight by FDA, by having information and intelligence that comes from other regulatory agencies who are also doing inspections and by having also local information from our local counterparts and the producers and suppliers.

So I was trying to explain to Mr. Dingell that, rather than simply responding to a formulaic number, that what I really think we need to do is create a much more strategic system of inspections that is tiered, that is risk-based, and that is focused on the particular issues of the product and its source.

Mr. BARTON. Well, that system that you just outlined, do you do that in the United States?

Dr. VON ESCHENBACH. Not to the degree that we need to and this is all consistent with what is really an integrated program.

Mr. BARTON. So this idea is something that would be relatively novel if implemented?

Dr. VON ESCHENBACH. Well, I think it is the modern FDA and it is based also on the importance of having an information technology infrastructure that supports all this.

Mr. BARTON. OK. Well, it is worth pursuing.

My final question, Mr. Chairman. Republican staff have been noodling some with their pencils and come up to do the foreign inspections that we think need to be done, we being Republican staff from the Subcommittee of Oversight and Investigation. It is going to take about 500 FDA inspectors additionally. Do you agree or disagree with that number and if you agree with it, how long do you think it would take to find and train those inspectors and get them in place overseas?

Dr. VON ESCHENBACH. I can't——

Mr. BARTON. That is just on a—that is not an official estimate. That is Mr. Shimkus' and my staff's best guess. It is not from some think tank that tens of millions of dollars went into to come up with.

Dr. VON ESCHENBACH. I can't refute the number. But it would have to be a phased-in approach to bring the number of people of that magnitude, more importantly, those skill sets.

Mr. BARTON. The number is in the ballpark?

Dr. VON ESCHENBACH. I am going to accept it is in the ballpark, yes.

Mr. BARTON. And do you have a time frame? You were getting ready to answer that and I cut you off. Two years, 5 years, 3 years?

Dr. VON ESCHENBACH. I believe that could be accomplished, as I indicated earlier, in an overall time frame of five at the outset. That particular process could be accomplished as early as perhaps three.

Mr. BARTON. My final question, are there any other countries that do foreign inspections like we are contemplating asking, directing the FDA to do? Do the Europeans have foreign inspections in place——

Dr. VON ESCHENBACH. Yes.

Mr. BARTON [continuing]. In China.

Dr. VON ESCHENBACH. Other—not necessarily do they have offices abroad, but they engage in foreign inspection.

Mr. BARTON. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Barton.

Mr. Commissioner, are you familiar with the program that was put in late 1990s with Europe, the mutual recognition agreement that they attempted to put in?

Dr. VON ESCHENBACH. I am aware of it, sir, but I am not familiar with all the details.

Mr. STUPAK. And what happened to that program?

Dr. VON ESCHENBACH. I apologize, I cannot answer that for you today.

Mr. STUPAK. I was on a committee for a while and it was under—Mr. Barton actually was the chairman and then we had a hearing in 1998 on it and basically it didn't work. This was with Europe, European Union, where we are supposed to do mutual inspections. In fact, it says under this arrangement the EU member states will be taking the place of FDA when it comes to inspections for good manufacturing practices.

Dr. VON ESCHENBACH. Yes.

Mr. STUPAK. Now if that program in the late 1990s didn't work with Europe, which is probably closer to us in culture and same standards and regulatory system, how on God's green Earth will it ever work in China, where we have very little in common? If Europe doesn't work, how is it going to work in China?

Dr. VON ESCHENBACH. Because I believe fundamentally the world is a lot different in 2008 than it was in 1998 and peoples' thinking is different. I've just recently even met a few days ago with growers.

Mr. STUPAK. Well, wouldn't we want to try to get back with Europe then?

Dr. VON ESCHENBACH. Pardon me.

Mr. STUPAK. Wouldn't it be easy to implement this agreement in Europe and in China? Why wouldn't we go back there and then the inspectors we are using in Europe we can use them in China and get to that 500 number that Mr. Barton talked about?

Dr. VON ESCHENBACH. One of the places that is included in FDA beyond our borders is Europe and working with our European counterparts——

Mr. STUPAK. So do you have an agreement like that in Europe?

Dr. VON ESCHENBACH [continuing]. Part of this effort. We haven't established the office in Europe but it is part of the plan.

Mr. STUPAK. Part of the plan, which hasn't worked yet and I don't see how it is going to work now.

Now let me ask you this, and I don't mean to be argumentative, draft legislation sent to your office a draft of our committee—latest copy of our food and drug inspection legislation. Have you seen this?

Dr. VON ESCHENBACH. Yes, sir, I have.

Mr. STUPAK. We sent it to your office. Are you prepared to comment on it at all?

Dr. VON ESCHENBACH. We are looking forward to working with you and Chairman Dingell and others on the Committee.

Mr. STUPAK. Yes, you say that all the time but you never comment on our legislation. We are trying to help you out here so——

Dr. VON ESCHENBACH. Well, my staff has had multiple interactions with the staff of the Committee, and we look forward to those continuing with the specifics of the bill.

Mr. STUPAK. We would like to know where the FDA stands on the bill, OK? It is going to be moving quickly, so—in fact one of the parts in there—let me just ask you a quick question. Isn't it true that foreign drug manufacturing firms can register with the FDA even if the firm does not intend on shipping products to the United States?

Dr. VON ESCHENBACH. Yes, sir.

Mr. STUPAK. And in order to do that you have to do an inspection and everything it costs us taxpayers, right? If you apply for—you go and do a pre-inspection, right?

Dr. VON ESCHENBACH. I believe that is correct, yes.

Mr. STUPAK. OK. According to the GAO, some of these manufacturers will register with the FDA as a marketing tool because the FDA registration might be seen as an endorsement of that plant by the FDA in some foreign markets. Are you aware of that?

Dr. VON ESCHENBACH. I have heard that alluded to.

Mr. STUPAK. And therefore, as in our legislation, wouldn't the sizable registration fee ensure that foreign establishments who register with the FDA are serious about actually exporting drugs to the United States? In other words, a sizable registration fee, would it weed out those firms who wish just to register so they can market products elsewhere and not to the United States?

Dr. VON ESCHENBACH. I can't comment whether that would be an adequate deterrent or not, sir.

Mr. STUPAK. They are gumming up your databases, aren't they, these firms that applied to get the U.S. certification, but they never ship; they are sitting in your database or just gumming up the IT system that we are having so much trouble with, are they not?

Dr. VON ESCHENBACH. Well, there may be important intelligence information about those firms that could be helpful to us. I don't know that it is gumming up the system, but they shouldn't—

Mr. STUPAK. What important intelligence information would be in the database?

Dr. VON ESCHENBACH. Pardon me.

Mr. STUPAK. What important intelligence information would be beneficial by having them sitting in your database that they never ship drugs to the United States?

Dr. VON ESCHENBACH. Well, maybe we would learn something about them that we would never want them to ship drugs into the United States.

Mr. STUPAK. Well, after you pre-approve them and they are registered, you would never know, because you don't go back and check them because they are not shipping to the United States.

Dr. VON ESCHENBACH. But by recognizing we might be able to cross-reference them with other databases that exist in our other counterparts around the world.

Mr. STUPAK. How many man-hours and the amount of resources have we spent on this heparin investigation, do you know?

Dr. VON ESCHENBACH. How many man-hours are spent what, sir?

Mr. STUPAK. On this heparin investigation thus far by the FDA. You have gone over and done an inspection over there, you have a couple reports on the 483, we got letters. How much time have you spent?

Dr. VON ESCHENBACH. I can't give you an exact hourly figure.

Mr. STUPAK. Give me a guesstimation. How many inspections could we have done if we would have—we have 90,000, 100,000 more?

Dr. VON ESCHENBACH. I couldn't give you that estimate, sir.

Mr. STUPAK. OK.

Dr. VON ESCHENBACH. Because I don't think they are exactly equivalent.

Mr. STUPAK. Well, if you had gone over and done the inspection which was never done in this plant before, you already did one inspection there, right, on heparin, that is approximately $45,000, you have a couple of people over there doing that, right?

Dr. VON ESCHENBACH. Well, the point—I thought the point of the question you asked me was what was the effort expenditure across FDA. The effort expenditure——

Mr. STUPAK. Correct.

Dr. VON ESCHENBACH [continuing]. Across FDA involved a whole host of people in a variety of places within the FDA. That wouldn't necessarily translate into those people doing inspections.

Mr. STUPAK. I see. But to give you more money to do things.

Let me just change gears here for a minute. FDA's primary goal here is to protect the public health. And let me ask you a question or two and then I'll—if anyone else wants to ask a question they can on any issue.

But this bisphenol A, BPA, OK, it is the chemical used in baby bottles and has terrible side effects. The National Toxicity Program at NIH has determined BPA may cause neural and behavioral problems as well as effects in the prostate gland, mammary gland at an early age for puberty in females. The Canadian Government has declared BPA to be toxic. The FDA continues to maintain that it is safe.

While the FDA has undertaken a formal transparent reassessment safety of BPA, to include those in Federal Register public comment and expert advisory panels, when do you expect to have some decision on BPA?

Dr. VON ESCHENBACH. Well, upon learning of the new data, new information, we immediately convened an interagency task force to address that new data scientifically, and that is in process and that will render our opportunity to make a decision. The Canadians are continuing their process of assessment with a commentary period. So we will be working with them, other counterparts, and our own internal scientific process, which is underway.

Mr. STUPAK. When do you expect to have a decision?

Dr. VON ESCHENBACH. I cannot tell you exactly when that decision will be made, because I don't know what the complexity of the analysis will involve, but it is underway.

Mr. STUPAK. Well, the Canadian Government has already pulled BPA as being toxic, as they labeled it in their country, so why has it taken us so much longer to get at this?

Dr. VON ESCHENBACH. I think again, Mr. Stupak, it is going to be based on what the science dictates and what the science tells us, and until we have that analysis——

Mr. STUPAK. Are you saying the Canadian Government wasn't based on science?

Dr. VON ESCHENBACH. What I am saying is that FDA is going to assess the science and make its own independent decision taking into account the information that is available from other sources like Canada.

Mr. STUPAK. Well, we would like some decisions soon on BPA. Our subcommittee is working on it and——

Dr. VON ESCHENBACH. We are acting upon this as we speak.

Mr. STUPAK. I have heard so many of those promises and they never come true. So I just want to make sure we have some date certain that you can give us when we could expect a decision on BPA.

Any questions, Mr. Shimkus, Mr. Burgess?

Mr. BURGESS. Yes, I could—just a couple of follow-ups on the line of questioning that you were pursuing, Mr. Chairman. Now, Dr. von Eschenbach, again we will cover the same ground, but inspectors in every location and every port in the People's Republic of China wouldn't have found that goop that got into the heparin, would it?

Dr. VON ESCHENBACH. No, sir.

Mr. BURGESS. Because we didn't know it was there. We didn't test for it. We didn't know to test for it.

Dr. VON ESCHENBACH. Correct.

Mr. BURGESS. Now the chairman also talks about how he is concerned that all of these extra applications coming into the IT systems are going to gum up the works. Are you at all concerned—when you think about gumming up the works that might be a little concern, but are you at all concerned about what we just did to the Agency with dumping tobacco in your lap? Because this is a huge new regulatory authority taken over by your agency that quite honestly we see that we are having trouble keeping up with what we are supposed to keep up with, and now we have got a product that when used as directed kills 400,000 people a year and you are going to certify that it is safe and effective? I mean, it is beyond goofy to think that that legislation makes sense with the crisis mode that the Food and Drug Administration is in right now. Again, it is our premier Federal agency and we are treating it with extreme disrespect by adding that regulatory requirement to what you are already doing.

And I don't expect you to answer that because I know that you are too smart to, but in today's Wall Street Journal you are quoted: The Food and Drug Administration Commissioner Andy von Eschenbach told Congress in October that the $5 billion in user fees over the next decade was not enough to kickstart a tobacco division, and the Food and Drug Administration may have to divert funds from its other programs.

Is that—did the Wall Street Journal get it right? Is that essentially correct?

Dr. VON ESCHENBACH. Well, I think the point of that was that the monies were not coming to the FDA. They were going to the

general treasury with the idea that you have pointed out—is that our resources and authorities have to be commensurate with our responsibilities, so that if we don't have the capability of carrying out those responsibilities then we will fail in our mission.

Mr. BURGESS. Again, your core mission is to—things have got to be safe and effective. So can we ever do that with tobacco? Can we ever say it is safe?

Dr. VON ESCHENBACH. Well, as a physician I know that there is no way that you can define a tobacco product as being safe. If used as directed, it produces the result of disease and death.

Mr. BURGESS. Well, now there was, I thought, a very insightful amendment offered during the markup process that would have allowed the Food and Drug Administration the authority to either ban tobacco outright or require that tobacco manufacturers produce a zero milligram nicotine cigarette. If you are going to have this authority, would you not think those two tools in your toolbox would be essential for securing the public health?

Dr. VON ESCHENBACH. Well, I believe there is a need for a lot of discussion about what tools are in the toolbox. As you pointed out, the significant issue of nicotine being the most—one of the most addictive substances that humans are exposed to, especially during development as teenagers are, that if you eliminated that completely you would eliminate the problem of addiction.

Mr. BURGESS. Thank you, Mr. Commissioner. I yield back the balance of my time.

Mr. STUPAK. Thanks. Mr. Melancon or Mr. Green? Mr. Shimkus.

Mr. SHIMKUS. Just have unanimous consent that I may submit some questions for the record and just for the statement say that if—I think a lot of the basic premise here is that if people want to sell goods and products to our citizens they need to meet our standards. And if you want to sell goods and services to our citizens, I think you ought to be willing to pay for that opportunity since we are the market everybody wants to get to. And, you know, it shouldn't be the burden placed upon taxpayers.

I also believe in trust, but verify when you have international agreements, and also that management by walking around or inspecting by walking around is still a basic practice that we all should observe and in this case that is our concern about not being involved in the factory.

Thank you, Mr. Chairman.

Mr. STUPAK. Thank you. You will be happy to know our legislation does include in there registration fees so taxpayers aren't paying for it. Please look at it. We are moving that legislation quickly.

Dr. von Eschenbach, thank you for your time. I hope you will stay for the next panel. As indicated earlier, they have 100 years of experience in these areas, and hopefully we can all benefit from their expertise. Thank you again for your time, sir.

Dr. VON ESCHENBACH. Thank you, Mr. Chairman. Just let me close by expressing I know what you share and other members of the Committee share. And that is, although we are talking about the many important changes that have to occur at FDA, some of the things that we must always preserve is the caliber and the quality of the incredible people that make up that agency. There are—half of the Agency are involved in our field activities and they

are doing heroic work, as you just alluded to with regard to our ability to immediately mitigate the problems associated with contaminated heparin. And so I thank you for our opportunities to present to you a vision for the future, and I appreciate your recognition of the incredible efforts that the people of FDA are making on behalf of the American people.

Mr. STUPAK. I agree with you, and the best way we can honor their work is to give them the resources they need so they can fully do their job.

Dr. VON ESCHENBACH. I agree with you. Thank you.

Mr. STUPAK. I would like to call up our second panel of witnesses and ask them to come forward here in a few moments. Gail Cassell, Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases at Eli Lilly and Company. Dr. Marcia Cross, Director of Public Health and Military Health Care Issues at the U.S. Government Accountability Office. Mr. William Hubbard, former FDA Associate Commissioner and current Senior Advisor to the Coalition for a Stronger FDA. Mr. Ben England of Benjamin England & Associates and FDAImports.com. Mr. England previously held several senior level regulatory positions at the FDA. And Dr. Carl Nielsen, retired Director of the Division of Import Operations within the Office of Regulatory Affairs at the FDA.

We will give everybody a minute or two here to assemble before we do the oath. It is the policy of the subcommittee to take all testimony under oath. Please be advised that witnesses have the right under the Rules of the House to be advised by counsel during their testimony. Do any of you wish to be represented by counsel? A shaking of the heads indicate no. Therefore, let's take the oath.

[Witnesses sworn.]

Mr. STUPAK. Let the record reflect that witnesses replied in the affirmative. You are now under oath.

We will now hear a 5-minute opening statement from each of our witnesses on the second panel. You may submit a longer statement for inclusion in the hearing record.

Dr. Cross, for the Government Accountability Office, shall we start with you, please?

**STATEMENT OF MARCIA G. CROSSE, DIRECTOR OF PUBLIC HEALTH AND MILITARY HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE**

Dr. CROSSE. Thank you, Mr. Chairman.

Mr. Chairman, members of the subcommittee, I am pleased to be here today as you examine FDA's foreign drug inspection program. I testified before this subcommittee last November on this topic. At that time I discussed how FDA's programs were not keeping up with the globalization of drug manufacturing. I testified about weaknesses in FDA's data systems, difficulties in prioritizing foreign establishments to inspect, infrequent inspections and challenges unique to conducting foreign inspections.

Slide, please. I have a slide. This slide shows the large mismatch between the number of foreign drug establishments and the number of inspections performed. As you can see, the largest mismatch is in China. Since the hearing in November, FDA has announced a number of initiatives to address these concerns, as we have heard

today from the Commissioner. You asked that we examine these and the extent to which they will fill the gaps we identified.

FDA's initiatives have the potential to strengthen FDA's foreign drug inspection program, but they do not fully address the weaknesses.

Let me discuss in turn the four key areas of concern we previously raised.

I testified in November that FDA's databases did not provide an accurate count of foreign establishments and provide widely divergent counts, with the result that FDA does not know how many foreign establishments are subject to inspection.

One recent FDA initiative is to require electronic registration to reduce inaccuracies in its registration database. However, this will not prevent erroneous registration by firms that do not manufacture for the U.S. market. Another initiative aimed at reducing duplication in its import database is a proposal that FDA has supported to change the data it receives from Customs and Border Protection on products entering the United States. However, the implementation of this proposal is not certain and would require actions from multiple Federal agencies in addition to FDA.

FDA has also begun efforts to integrate its various databases. This could provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell how much it will help and this effort has not been fully funded. In fact, FDA officials told us that implementation has been slow because the Agency has been forced to shift resources away from the improvements in order to maintain the current systems.

Next I testified that gaps in information weaken FDA's processes for prioritizing the inspection of foreign establishments that pose the greatest risk to public health. FDA lacks key information on many foreign establishments. This limits its ability to use its risk-based approach to select establishments for inspection.

To address this, FDA has discussed obtaining useful information such as inspection reports from foreign regulatory bodies. However, the Agency already has a number of such agreements in place and it has faced challenges in using these arrangements in the past. For example, FDA had difficulties in determining whether the scope of other countries' inspections met its needs and inspection reports were not always readily available in English. FDA also told us that complete reliance on another country's inspection results is risky. The result has been that FDA only used its existing arrangements six times in the past year. This raises concerns about some of the proposals the Commissioner has discussed to rely on inspections from others.

I also testified in November that FDA inspected relatively few foreign establishments each year. And at the current rate it would take FDA more than 13 years to inspect all foreign establishments just once. FDA slightly increased the number of foreign drug inspections in fiscal year 2007, but the Agency still inspects foreign establishments at a substantially lower rate than domestic establishments.

The foreign inspections shown in the figure are the largest number that FDA has ever conducted. FDA's budget calls for incremental increases in funding for foreign inspections. FDA dedicated

about $10 million to foreign drug inspections in fiscal year 2007 and plans to dedicate about $11 million to such inspections in fiscal year 2008. However, it would cost about $70 million per year to perform biennial inspections of foreign establishments, as is already required for domestic establishments. The $11 million FDA plans to spend this year for all foreign drug inspections falls short of the $16 million that would be needed each year just to conduct biennial inspections in China.

Finally, I testified that FDA faced certain logistical and staffing challenges unique to conducting foreign inspections, including reliance on volunteer inspectors and a lack of translators. FDA has proposed establishing a dedicated cadre of staff to conduct foreign inspections, but the overall time frame associated with this initiative is unclear.

FDA has also announced plans to establish offices overseas with an initial eight FDA staff to be based in China and five Chinese nationals to provide translation and logistical support. However, the impact that these offices will have on the foreign drug inspection program is unknown because these staff would be responsible for all FDA regulated products.

In China, in addition to the estimated 714 drug establishments, there are an estimated 675 medical device establishments and many more firms manufacturing food and other FDA-regulated products subject to inspection. The agreement with China is not finalized and plans for other countries are still in development.

In conclusion, Americans depend on FDA to ensure the safety and effectiveness of the drugs they take. The recent incident involving heparin underscores the importance of FDA's initiatives. FDA's actions, if fully implemented, could address some of the concerns we identified. Given the growth in foreign drug manufacturing for the U.S. market and the relatively few foreign inspections conducted by FDA, the Agency will need to devote considerable resources to this area if it is to increase the rates of inspections. However, FDA's incremental increases will have little impact in the near future to reduce the interval between inspections for these establishments.

In addition, many of FDA's initiatives will take several years to implement and require funding and certain interagency or intergovernmental agreements that are not yet in place. Taken together, FDA's plans represent a step forward in filling the large gaps in FDA's foreign drug inspection program, but do little to accomplish short-term change.

Mr. Chairman, this concludes my prepared remarks. I will be happy to answer any questions that you or other members of the subcommittee may have.

[The prepared statement of Dr. Crosse follows:]

United States Government Accountability Office

GAO

Testimony

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

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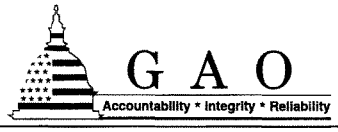
# DRUG SAFETY

# Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program

Statement of Marcia Crosse, Director
Health Care




GAO-08-701T

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# Highlights

Highlights of GAO-08-701T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

April 22, 2008

## DRUG SAFETY

## Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program

### Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments. FDA inspects foreign establishments to ensure that they meet the same standards required of domestic establishments. Ongoing concerns regarding FDA's foreign drug inspection program recently were heightened when FDA learned that contaminated doses of a common blood thinner had been manufactured at a Chinese establishment that the agency had never inspected. FDA has announced initiatives to improve its foreign drug inspection program.

In November 2007, GAO testified on weaknesses in FDA's foreign drug inspection program (GAO-08-224T). This statement presents preliminary findings on how FDA's initiatives address the weaknesses GAO identified. GAO interviewed FDA officials and analyzed FDA's initiatives. GAO examined reports and proposals prepared by the agency, as well as its plans to improve databases it uses to manage its foreign drug inspection program.

To view the full product, including the scope and methodology, click on GAO-08-701T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

### What GAO Found

Recent FDA initiatives—some of which have been implemented and others proposed—could strengthen FDA's foreign drug inspection program, but these initiatives do not fully address the weaknesses that GAO previously identified.

- GAO testified in November 2007 that FDA's databases do not provide an accurate count of foreign establishments subject to inspection and do provide widely divergent counts. Through one recent initiative, FDA has taken steps to improve its database intended to include foreign establishments registered to market drugs in the United States. This initiative may reduce inaccuracies in FDA's count of foreign establishments. However, these steps will not prevent foreign establishments that do not manufacture drugs for the U.S. market from erroneously registering with FDA. Further, to reduce duplication in its import database, FDA has supported a proposal that would change the data it receives on products entering the United States. However, the implementation of this proposal is not certain and would require action from multiple federal agencies, in addition to FDA. Efforts to integrate these databases have the potential to provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell.

- GAO testified that gaps in information weaken FDA's processes for prioritizing the inspection of foreign establishments that pose the greatest risk to public health. While FDA recently expressed interest in obtaining useful information from foreign regulatory bodies that could help it prioritize foreign establishments for inspections, the agency has faced difficulties fully utilizing these arrangements in the past. For example, FDA had difficulties in determining whether the scope of other countries' inspection reports met its needs and these reports were not always readily available in English.

- GAO also testified that FDA inspected relatively few foreign establishments each year. FDA made progress in inspecting more foreign establishments in fiscal year 2007, but the agency still inspects far fewer of them than domestic establishments. FDA dedicated about $10 million to foreign drug inspections in fiscal year 2007 and plans to dedicate about $11 million to such inspections in fiscal year 2008.

- Finally, GAO testified that FDA faced certain logistical and staffing challenges unique to conducting foreign inspections. FDA is pursuing initiatives that could address some of the challenges that we identified as being unique to foreign inspections, such as volunteer inspection staff and lack of translators. FDA has proposed establishing a dedicated cadre of staff to conduct foreign inspections, but the timeframe associated with this initiative is unclear. FDA plans to open an office in China and is considering establishing offices in other countries, but the impact that this will have on the foreign drug inspection program is unknown.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you consider the Food and Drug Administration's (FDA) plans to improve its program for inspecting foreign drug manufacturers whose products are marketed in the United States. America has become increasingly dependent on drugs and drug ingredients manufactured in foreign countries. Ten years ago, we reported that FDA needed to improve its foreign drug inspection program.[1] Among other things, we noted that FDA had serious problems managing its foreign inspection data. We were also critical of the number of inspections FDA conducted at foreign manufacturers. In November 2007, we testified on the preliminary findings of our current work in which we identified weaknesses similar to those we found in our previous report.[2] Our preliminary findings suggested that FDA had weaknesses in its databases, including conflicting information on the number of foreign establishments subject to inspection;[3] had information gaps that weakened its process for selecting foreign establishments for inspection; conducted infrequent inspections of these establishments; and faced logistical and staffing challenges unique to foreign inspections. Recent developments involving heparin sodium, a commonly used blood thinner, have further heightened concerns about the safety of drugs and drug ingredients and FDA's ability to inspect foreign manufacturers of these products. In January 2008, FDA began an investigation after receiving reports of serious adverse events in people receiving this drug. The agency later learned that an active pharmaceutical ingredient (API) found in heparin sodium contained a

[1]GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: Mar. 17, 1998).

[2]GAO, *Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, GAO-08-224T (Washington, D.C.: Nov. 1, 2007). We also recently testified about similar weaknesses that we identified in FDA's program for inspecting foreign medical device manufacturers. GAO, *Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections*, GAO-08-428T (Washington, D.C.: Jan. 29, 2008).

[3]FDA regulations define an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.3(a)(7) (2007). Drug firms may have more than one establishment.

contaminant and had been manufactured at a Chinese establishment never inspected by FDA.[4]

Recently, FDA has begun or proposed initiatives to strengthen its foreign drug inspection program.[5] You asked us to assess whether FDA's initiatives will improve its management of this program. My testimony today will focus on these initiatives and how they address the weaknesses we previously identified.

To obtain information about FDA initiatives and how they address weaknesses in its program for inspecting foreign drug manufacturers, we interviewed officials from FDA, including from its Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign inspection program. We examined reports and proposals prepared by the agency on related initiatives. We also examined FDA's plans to improve databases it uses to manage its foreign drug inspection program, including its Field Accomplishments and Compliance Tracking System (FACTS), Operational and Administrative System for Import Support (OASIS), and Drug Registration and Listing System (DRLS).[6] Our November 2007 testimony included the number of inspections from FACTS as of September 26, 2007. To provide information to update those preliminary findings, we obtained FACTS data that contained information on fiscal year 2007 inspections conducted or entered into this database since our previous analysis. We also obtained fiscal year 2007 data from OASIS to determine the types of drug products manufactured in China and offered for entry into the United States. We assessed the reliability of these databases by (1) reviewing existing information about the data and the databases that produced them,

[4]An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product. According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis.

[5]See, for example, Food and Drug Administration, *Revitalizing ORA: Protecting the Public Health Together In a Changing World* (Rockville, Md.: Jan. 2008).

[6]We also previously examined the reliability of DRLS. We found that DRLS was reliable, to the extent that it accurately reflects information provided by foreign drug manufacturing establishments that register with FDA. However, we determined that these data do not necessarily reflect all foreign establishments whose drugs are imported into the United States. We do not present new information from DRLS in this testimony.

(2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of required data elements. We found the data in the FACTS database reliable for our purposes. In addition, we found that while OASIS is likely to over-estimate the number of foreign establishments involved in the manufacture of those drugs because of uncorrected errors in the data, it provides sufficiently reliable information about the types of drugs offered for entry into the United States. The information we present represents the best information available and is what FDA relies on to manage its foreign drug inspection activities. Our ongoing work is focused on human drugs regulated by CDER and not on biologics,[7] medical devices, veterinary medicines, food, or other items or products for which FDA conducts inspections. However, we obtained information from the center responsible for medical devices, the Center for Devices and Radiological Health (CDRH), to learn about a recent change to one of its databases that addresses problems similar to those in DRLS. We shared the facts contained in this statement with FDA officials. They provided technical comments, which we incorporated as appropriate. We conducted the work for our November 2007 testimony from September 2007 through October 2007, and we conducted our work for this statement from March 2008 through April 2008. All of our work is being performed in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

In summary, recent FDA initiatives—some of which have been implemented and others proposed—could strengthen FDA's foreign drug inspection program, but these initiatives do not fully address the weaknesses that we previously identified. For example, we found that FDA's databases do not provide an accurate count of foreign establishments subject to inspection. FDA plans to implement electronic registration for foreign establishments. Implementing such a process may reduce inaccuracies in FDA's database of registered establishments. However, this will not prevent foreign establishments that do not manufacture drugs for the U.S. market from erroneously registering with

[7]Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Some biologics are regulated by CDER and inspections related to those products are included in our work.

FDA. For example, in some foreign markets, foreign drug manufacturers may register with FDA because registration may appear to convey an "approval" or endorsement by the agency. To reduce duplication in FDA's import database, FDA supported a proposal to create a unique governmentwide identifier for all establishments whose products are imported into the United States. However, the implementation of this identifier is not certain and would require action from multiple federal agencies in addition to FDA. Efforts to integrate these databases have the potential to provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell. FDA has also taken steps that could help it select foreign establishments for inspection by obtaining information from foreign regulatory bodies. However, the agency has not fully utilized arrangements with foreign regulatory bodies in the past that would allow it to obtain such information. FDA has also made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA is pursuing initiatives that could address some of the challenges that we identified as unique to foreign inspections. For example, the agency has proposed establishing overseas offices, beginning in China, but the impact that these offices will have on the foreign drug inspection program is unknown. To date, it is unclear whether the agency's proposals will increase the frequency with which FDA inspects foreign establishments or the quality of information it uses to select establishments to inspect.

## Background

FDA is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments.[8] Foreign establishments that market their drugs in the United States must register with FDA. As part of its efforts to ensure the safety and quality of imported drugs, FDA may inspect foreign establishments whose products are imported into the United States. Regular inspections of manufacturing establishments are an essential component of ensuring drug safety. Conducting testing of finished dosage form drug products cannot reliably determine drug quality. Therefore, FDA relies on inspections to determine an establishment's compliance with current good manufacturing practice regulations (GMP).[9] These inspections are a critical mechanism in FDA's

[8]FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 C.F.R. § 207.3(a)(8) (2007).

[9]GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality products. See 21 C.F.R. pts. 210, 211 (2007).

process of assuring that the safety and quality of drugs are not jeopardized by poor manufacturing practices.

Requirements governing foreign and domestic inspections differ. Specifically, FDA is required to inspect every 2 years those domestic establishments that manufacture drugs marketed in the United States,[10] but there is no comparable requirement for inspecting foreign establishments. FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to conduct physical examinations of products offered for import, and if there is sufficient evidence of a violation, prevent their entry at the border.

Within FDA, CDER sets standards and evaluates the safety and effectiveness of prescription and over-the-counter drugs. Among other things, CDER requests that ORA inspect both foreign and domestic establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including current GMPs. CDER requests that ORA conduct inspections of establishments that produce drugs in finished-dosage form as well as those that produce bulk drug substances,[11] including APIs used in finished drug products. These inspections are performed by investigators and, on occasion, laboratory analysts.[12] ORA conducts two primary types of drug manufacturing establishment inspections:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States.[13] These inspections occur following FDA's receipt of a new drug application (NDA) or an abbreviated new drug application (ANDA)

[10]21 U.S.C. § 360(h).

[11]A bulk drug substance is any substance that is represented for use in a drug that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished drug product. 21 C.F.R. § 207.3(a)(4) (2007).

[12]ORA investigators lead inspections. Investigators are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing.

[13]When FDA receives an application for drug approval, officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the application has received a satisfactory GMP inspection in the 2 previous years and the agency has no new concerns, FDA will consider this inspection sufficient and will not perform a preapproval inspection of this establishment.

and focus on the manufacture of a specific drug.[14] Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the manufacturer is following commitments made in the application. FDA also determines that the manufacturer of the finished drug product, as well as each manufacturer of a bulk drug substance used in the finished product, manufactures, processes, packs, and labels the drug adequately to preserve its identity, strength, quality, and purity.

- Postapproval GMP surveillance inspections are conducted to ensure ongoing compliance with the laws and regulations pertaining to the manufacturing processes used by domestic and foreign establishments in the manufacture of drug products marketed in the United States and bulk drug substances used in the manufacture of those products. These inspections focus on a manufacturer's systemwide controls for ensuring that drug products are of high quality. Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drug products.[15]

FDA has established arrangements with regulatory bodies in other countries to facilitate the sharing of information about drug inspections. FDA has entered into arrangements related to GMP inspections with Canada, Japan, the European Union, and others. The scope of such arrangements can vary. Some arrangements may allow FDA to obtain reports of inspections conducted by other countries, for informational purposes. Other arrangements may involve more than the exchange of information. For example, FDA and another country may enter into an arrangement to work towards the mutual recognition of each other's inspection standards or the acceptance of one another's inspections, in lieu of their own.

[14]FDA must approve an NDA in order for a new drug to be marketed in the United States. FDA reviews scientific and clinical data contained in these applications as part of its process in considering them for approval to be marketed. Approval for a generic drug is sought through an ANDA.

[15]In addition, FDA conducts for-cause inspections when it receives information indicating problems in the manufacture of approved drug products, as well as when it follows up on manufacturers that were not in compliance with GMPs during previous inspections.

CDER uses a risk-based process to select some foreign and domestic establishments for postapproval GMP surveillance inspections. The process uses a risk-based model to identify those establishments that, based on characteristics of the establishment and of the product being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. For example, FDA considers the risk to public health from poor quality over-the-counter drugs to be lower than for prescription drugs. Consequently establishments manufacturing only over-the-counter drugs receive a lower score on this factor in the risk-based process than other manufacturers. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments.

FDA uses multiple databases to manage its foreign drug inspection program.

- DRLS contains information on foreign and domestic drug establishments that have registered with FDA to market their drugs in the United States. These establishments must also list any drugs they market in the United States. These establishments provide information, such as company name and address and the drug products they manufacture for commercial distribution in the United States, on paper forms, which are entered into DRLS by FDA staff.

- OASIS contains information on drugs and other FDA-regulated products offered for entry into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by Customs and Border Protection (CBP). The data are originally entered by customs brokers based on the information available from the importer.[16] CBP specifies an algorithm by which customs brokers generate a manufacturer identification number from information about an establishment's name, address, and location.

- FACTS contains information on FDA's inspections of foreign and domestic drug establishments. FDA investigators and laboratory analysts enter information into FACTS following completion of an inspection.

[16]Customs brokers are private individuals, partnerships, associations, or corporations licensed, regulated, and empowered by CBP to assist in meeting federal requirements governing imports and exports.

According to DRLS, in fiscal year 2007, foreign countries that had the largest number of registered establishments were Canada, China, France, Germany, India, Italy, Japan, and the United Kingdom. These countries are also listed in OASIS as having the largest number of manufacturers offering drugs for entry into the United States. Specifically, according to OASIS, China had more establishments manufacturing drugs that were offered for entry into the United States than any other country. According to OASIS, in fiscal year 2007, a wide variety of prescription and over-the-counter drug products manufactured in China were offered for entry into the United States, including pain killers, antibiotics, blood thinners, and hormones.

In November 2007, we testified on preliminary findings that identified weaknesses in FDA's program for inspecting foreign establishments manufacturing drugs for the U.S. market. Specifically, we found that, as in 1998, FDA's effectiveness in managing the foreign drug inspection program continued to be hindered by weaknesses in its data on foreign establishments. FDA did not know how many foreign establishments were subject to inspection. FDA relied on databases that were designed for purposes other than managing the foreign drug inspection program. Further, these databases contained inaccuracies that FDA could not easily reconcile. DRLS indicated there were about 3,000 foreign establishments registered with FDA in fiscal year 2007,[17] while OASIS indicated that about 6,800 foreign establishments actually offered drugs for entry in that year. FDA recognized these inconsistencies, but could not easily correct them partly because the databases could not exchange information. Any comparisons of the data must be performed manually, on a case-by-case basis.

We also testified that FDA inspected relatively few foreign establishments.[18] Data from FDA suggested that the agency may inspect about 8 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection. However, FDA could not provide an exact number of foreign

[17]This count includes foreign establishments that were registered to manufacture human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

[18]We updated information presented in our November 2007 testimony because that data did not include complete counts of inspections conducted in fiscal year 2007.

establishments that had never been inspected. From fiscal year 2002 through fiscal year 2007, FDA conducted 1,479 inspections of foreign establishments, and three quarters of these inspections were concentrated in 10 countries. (See table 1.) Because some establishments were inspected more than once during this time period, FDA actually inspected 1,119 unique establishments. For example, of the 94 inspections that FDA conducted of Chinese establishments, it inspected 80 unique establishments across this six year period. The lowest rate of inspections in these 10 countries was in China, for which FDA inspected 80 of its estimated 714 establishments, or fewer than 14 establishments per year, on average.

**Table 1: Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Market, by Country for the 10 Most Frequently Inspected Countries, Fiscal Year 2002 through Fiscal Year 2007**

| | Number of inspections | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Country | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007 | Total | Number of unique establishments inspected | Number of establishments* |
| India | 11 | 19 | 38 | 33 | 34 | 64 | **199** | 152 | 410 |
| Germany | 24 | 15 | 35 | 25 | 19 | 25 | **143** | 95 | 199 |
| Italy | 17 | 30 | 26 | 21 | 18 | 28 | **140** | 98 | 150 |
| Canada | 29 | 12 | 17 | 23 | 23 | 20 | **124** | 88 | 288 |
| United Kingdom | 17 | 21 | 15 | 18 | 15 | 16 | **102** | 84 | 169 |
| China | 11 | 9 | 17 | 21 | 17 | 19 | **94** | 80 | 714 |
| France | 14 | 15 | 13 | 12 | 16 | 24 | **94** | 71 | 162 |
| Japan | 11 | 13 | 14 | 21 | 13 | 22 | **94** | 82 | 196 |
| Switzerland | 12 | 12 | 11 | 17 | 9 | 17 | **78** | 50 | 83 |
| Ireland | 11 | 5 | 11 | 14 | 3 | 14 | **58** | 43 | 61 |
| All other countries | 63 | 38 | 63 | 61 | 45 | 83 | **353** | 276 | 817 |
| **Total** | **220** | **189** | **260** | **266** | **212** | **332** | **1,479** | **1,119** | **3,249** |

Source: GAO analysis of FDA data.

*This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections. In preparing this list, FDA draws on information from DRLS. It also obtains information from previous inspections to help it identify establishments that are subject to inspection but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. However, as a result of the inaccuracies in DRLS, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

We testified that, while enforcing GMP compliance through surveillance inspections was FDA's most comprehensive program for monitoring the quality of marketed drugs, most of FDA's inspections of foreign manufacturers occurred when they were listed in an NDA or ANDA. The majority of these preapproval inspections were combined with a GMP surveillance inspection. Although FDA used a risk-based process to develop a prioritized list of foreign establishments for GMP surveillance inspections, few were completed in a given year—about 30 in fiscal year 2007. The usefulness of the process was weakened by the incomplete and possibly inaccurate information on those foreign establishments that FDA had not inspected recently, as well as those that had never been the subject of a GMP surveillance inspection.

We also testified that FDA's foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered. Finally, language barriers can make foreign inspections more difficult than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

## Recent Initiatives May Help FDA Select Foreign Establishments for Inspection, but Weaknesses in Its Foreign Drug Inspection Program Are Not Fully Addressed

FDA has initiated several recent changes to its foreign drug inspection program, but the changes do not fully address the weaknesses that we previously identified. FDA has initiatives underway to reduce the inaccuracies in its registration and import databases that make it difficult to determine the number of foreign establishments subject to inspection, although to date these databases still do not provide an accurate count of such establishments. FDA has taken steps that could help it select foreign establishments for inspection by obtaining information from foreign regulatory bodies. However, the agency has not fully utilized arrangements with foreign regulatory bodies in the past that would allow it to obtain such information. FDA has made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA is also pursuing initiatives that could address some of the challenges that we identified as being unique to foreign inspections, but implementation details and timeframes associated with these initiatives are unclear.

## FDA Initiatives Could Improve Its Data, but Will Not Ensure an Accurate Count of Foreign Establishments Subject to Inspection

FDA has initiatives underway to reduce inaccuracies in its databases, but actions taken thus far will not ensure that the agency has an accurate count of establishments subject to inspection. As we previously testified, DRLS does not provide FDA with an accurate count of foreign establishments manufacturing drugs for the U.S. market. For example, foreign establishments may register with FDA, whether or not they actually manufacture drugs for the U.S. market,[19] and the agency does not routinely verify the information provided by the establishment. Beginning in late 2008, CDER plans to implement an electronic registration and listing system that could improve the accuracy of information the agency maintains on registered establishments. The new system will allow drug manufacturing establishments to submit registration and listing information electronically, rather than submitting it on paper forms. FDA hopes that electronic registration will result in efficiencies allowing the agency to shift resources from data entry to assuring the quality of the databases. However, electronic registration alone will not prevent foreign establishments that do not manufacture drugs for the U.S. market from registering, thus still presenting the problem of an inaccurate count.

Recently, another FDA center implemented changes affecting the registration of medical device manufacturers, an activity for which we previously identified problems similar to those found in CDER.[20] In fiscal year 2008, CDRH implemented, in addition to electronic registration, an annual user fee of $1,706 per registration for certain medical device establishments[21] and an active re-registration process.[22] According to CDRH, as of early April 2008, about half of the previously registered establishments have reregistered using the new system. While CDRH

[19]FDA officials pointed out that some foreign establishments register, for example, because registration may erroneously appear to convey an "approval" or endorsement by FDA in foreign markets.

[20]GAO, *Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections*, GAO-08-428T (Washington, D.C.: Jan. 29, 2008).

[21]21 U.S.C. §§ 379i(13); 379j(a)(3), (b), (h). The registration user fee is $1,706 in fiscal year 2008 and will increase by 8.5 percent per year, to $2,364 in fiscal year 2012. Fees are available for obligation only to the extent and in the amount provided in annual appropriations acts. FDA's authority to assess registration fees terminates on October 1, 2012.

[22]CDRH indicated that the center will deactivate the registrations of those establishments that fail to complete the annual registration. Officials noted that, in the past, many establishments that had previously registered had not updated those registrations in several years.

officials expect that this number will increase,[23] they expect that the elimination of establishments that do not manufacture medical devices for the U.S. market—and thus should not be registered—will result in a smaller, more accurate database of medical device establishments. CDRH officials indicated that implementation of electronic registration and the annual user fee seems to have improved the data so CDRH can more accurately identify the type of establishment registered, the devices manufactured at an establishment, and whether or not an establishment should be registered. According to CDRH officials, the revenue from device registration user fees is applied to the process for the review of device applications,[24] including establishment inspections undertaken as part of the application review process. CDER does not currently have the authority to assess a user fee for registration of drug establishments, but officials indicated that such a fee could discourage registrations of foreign manufacturers that are not ready, are not actively importing, or have not been approved to market drug products in the United States. Officials also suggested that such fees could be used to supplement the resources available for conducting inspections.

FDA has proposed, but not yet implemented, the Foreign Vendor Registration Verification Program, which could help improve the accuracy of information FDA maintains on registered establishments. Through this program, FDA plans to contract with an external organization to conduct on-site verification of the registration data and product listing information of foreign establishments shipping drugs and other FDA-regulated products to the United States. As of April 2008, FDA had solicited proposals for this contract but was still developing the specifics of the program. For example, the agency had not yet established the criteria it would use to determine which establishments would be visited for verification purposes or determined how many establishments it would verify annually. FDA currently plans to award this contract in May 2008. Given the early stages of this process, it is too soon to determine whether this program will improve the accuracy of the data FDA maintains on foreign drug establishments.

[23]According to CDRH, in April, the center will send letters to establishments that have registered in the past but have not completed their registration for fiscal year 2008 advising them that they must register using the new system and must pay the registration fee, if applicable, to be considered registered.

[24]21 U.S.C. § 379i(8).

In addition to changes to improve DRLS, FDA has supported a proposal that has the potential to address weaknesses in OASIS, but FDA does not control the implementation of this change. As we previously testified, OASIS contains an inaccurate count of foreign establishments manufacturing drugs imported to the United States as a result of unreliable identification numbers generated by customs brokers when the product is offered for entry.[25] FDA officials told us that these errors result in the creation of multiple records for a single establishment, which results in inflated counts of establishments offering drugs for entry into the U.S. market. FDA is pursuing the creation of a governmentwide unique establishment identifier, as part of the Shared Establishment Data Service (SEDS), to address these inaccuracies.[26] Rather than relying on the creation and entry of an identifier at the time of import, SEDS would provide a unique establishment identifier and a centralized service to provide commercially verified information about establishments. The standard identifier would be submitted as part of import entry data where required by FDA or other government agencies. SEDS could thus eliminate the problem of having multiple identifiers associated with an individual establishment. The implementation of SEDS is dependent on action from multiple federal agencies, including the integration of the concept into a CBP import and export system currently under development and scheduled for implementation in 2010. In addition, once implemented by CBP, participating federal agencies would be responsible for bearing the cost of integrating SEDS with their own operations and systems. FDA officials are not aware of a specific timeline for the implementation of SEDS. Developing an implementation plan for SEDS is a recommendation of the Interagency Working Group on Import Safety's *Action Plan for Import Safety: A Roadmap for Continual Improvement.*

Finally, FDA is in the process of implementing additional initiatives to improve the integration of its current data systems, which could make it easier for the agency to establish an accurate count of foreign drug manufacturing establishments subject to inspection. The agency's Mission Accomplishments and Regulatory Compliance Services (MARCS) is intended to help FDA electronically integrate data from multiple systems.

[25]The algorithm currently used by customs broker to assign the manufacturer identification number does not provide for a number that is reliably reproduced or inherently unique.

[26]The SEDS concept was developed by a working group with representatives from FDA, the Environmental Protection Agency, and the departments of Agriculture, Commerce, Defense, and Homeland Security.

It is specifically designed to give individual users a more complete picture of establishments. FDA officials estimate that MARCS, which is being implemented in stages, could be fully implemented by 2011 or 2012. However, FDA officials told us that implementation has been slow because the agency has been forced to shift resources away from MARCS and toward the maintenance of current systems that are still heavily used, such as FACTS and OASIS. Taken together, electronic registration, the Foreign Vendor Registration Verification Program, SEDS, and MARCS could provide the agency with more accurate information on the number of establishments subject to inspection. However, it is too early to tell.

## FDA Initiatives to Obtain Information on Foreign Establishments May Have Limited Impact on Its Selection of Establishments to Inspect

FDA has taken steps to help it select establishments for inspection by obtaining information on foreign establishments from regulatory bodies in other countries, despite encountering difficulties in fully utilizing these arrangements in the past. FDA has recognized the importance of receiving information about foreign establishments from other countries and has taken steps to develop new, or strengthen existing, information-sharing arrangements to do so. For example, according to FDA, the agency is enhancing an arrangement to exchange information with the Swiss drug regulatory agency. FDA officials have highlighted such arrangements as a means of improving the agency's oversight of drugs manufactured in foreign countries. For example, they told us that in selecting establishments for GMP surveillance inspections, they sometimes use the results of an establishment inspection conducted by a foreign government to determine whether to inspect an establishment.[27] FDA told us that it received drug inspection information from foreign regulatory bodies six times in 2007.

FDA has previously encountered difficulties which prevented it from taking full advantage of information-sharing arrangements with other countries. Obtaining inspection reports from other countries and using this information has proved challenging. In order for FDA to determine the value of inspection reports from a particular country, it must consider whether the scope of that country's inspections is sufficient for FDA's needs. Evaluation of inspections conducted by foreign regulatory bodies can be complex and may include on-site review of regulatory systems and audit inspections. Further, to obtain results of inspections conducted by

[27]FDA officials told us that they do not use the results of an inspection conducted by a foreign regulatory body to make decisions about whether to approve a new drug.

its foreign counterparts, FDA must specifically request them—they are not automatically provided. While FDA has provided certain foreign regulatory bodies access to its Compliance Status Information System—which provides information from the results of FDA's inspections—foreign regulatory bodies have not established similar systems to provide FDA access to data about their inspections. FDA indicated that such systems are under development in some countries and FDA has been promised access when they are available. However, currently, FDA cannot routinely incorporate the results of inspections conducted by foreign regulatory authorities into its risk-based selection process.[28] FDA officials stated that, in the past, they encountered difficulties using inspection reports from other countries that were not readily available in English. Consequently, the existence of such information-sharing arrangements alone may not help FDA systematically address identified weaknesses in its foreign inspection program.

Arrangements that have the potential to allow FDA to formally accept the results of inspections conducted by other countries have been prohibitively challenging to implement. Although these arrangements allow countries to leverage their own inspection resources, according to FDA officials, assessing the equivalence of other countries' inspections and the relevance of the information available is difficult. They added that complete reliance on another country's inspection results is risky. The activities associated with establishing these agreements may be resource intensive, which may slow FDA's implementation of them. For example, FDA told us that a lack of funding for establishing such an arrangement with the European Union effectively stopped progress. Although FDA has completed preliminary work associated with this arrangement, the agency has concluded that it will be more beneficial to pursue other methods of cooperating with the European Union. The agency has no plans at this time to enter into other such arrangements.

FDA's current efforts to obtain more information from foreign regulatory bodies may help it better assess the risk of foreign establishments when prioritizing establishments for GMP surveillance inspections. However, most foreign inspections are conducted to examine an establishment referenced in an NDA or ANDA. The agency conducts relatively few

[28]In addition to challenges in obtaining inspection reports, FDA may also be limited by the type of information available. For example, FDA may not be able to obtain inspection reports on API manufacturing establishments because other regulatory bodies may only inspect finished-dosage manufacturers.

foreign GMP surveillance inspections selected through its risk-based process. Therefore, these efforts may be of limited value to the foreign inspection program if the agency does not increase the number of such inspections.

## FDA Has Increased Its Inspections of Foreign Establishments, but Still Inspects Relatively Few

FDA has made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA conducted more foreign establishment inspections in fiscal year 2007 than it had in each of the 5 previous fiscal years. However, the agency still inspected less than 11 percent of the foreign establishments on the prioritized list that it used to plan its fiscal year 2007 GMP surveillance inspections.[29] The agency also still conducts far fewer inspections of foreign establishments than domestic establishments. Its budget calls for incremental increases in funding for foreign inspections. FDA officials told us that, for fiscal year 2008, the agency plans to conduct more GMP surveillance inspections based on its prioritized list of foreign establishments. FDA officials estimated that the agency conducted about 30 such inspections in fiscal year 2007 and plans to conduct at least 50 in fiscal year 2008.

If FDA were to inspect foreign establishments biennially, as is required for domestic establishments, this would require FDA to dedicate substantially more funding than it has dedicated to such inspections in the past. In fiscal year 2007, FDA dedicated about $10 million to inspections of foreign establishments.[30] FDA estimates that, based on the time spent conducting inspections of foreign drug manufacturing establishments in fiscal year 2007, the average cost of such an inspection ranges from approximately $41,000 to $44,000.[31] Our analysis suggests that it could cost the agency $67 million to $71 million each year to biennially inspect each of the 3,249 foreign drug establishments on the list that FDA used to plan its fiscal year 2007 GMP surveillance inspections. Based on these same estimates, it would take the agency $15 million to $16 million each year to inspect the estimated 714 drug manufacturing establishments in China

[29]As a result of the inaccuracies in its data, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

[30]According to FDA budget documents, the agency dedicated about $43 million to inspecting domestic drug manufacturers in fiscal year 2007.

[31]According to FDA, the cost of conducting foreign inspections varies, depending on whether the type of inspection was a preapproval or GMP surveillance inspection, by the time spent at an establishment, by the number of FDA staff conducting the inspection, and by the costs associated with traveling to the country in which the establishment is located.

every 2 years. According to FDA budget documents, the agency estimates that it will dedicate a total of about $11 million in fiscal year 2008 and $13 million in fiscal year 2009 to all foreign inspections.

In its fiscal year 2009 budget, FDA proposed instituting a reinspection user fee.[32] Reinspections are conducted to verify that corrective actions the agency has required establishments to take in response to previously identified violations have been implemented. FDA's proposal to institute a reinspection user fee would allow it to charge establishments a fee when the agency determines a reinspection is warranted. However, as proposed, the reinspection user fee would be budget neutral, meaning that the other appropriated funds the agency receives would be offset by the amount of collected reinspection fees. As a result, this proposal would not provide the agency with an increase in funds that could be used to pay for additional foreign inspections.

## FDA Initiatives May Address Some Challenges Unique to Foreign Inspections, but It Is Too Early to Determine Their Effectiveness

FDA has recently announced proposals to address some of the challenges unique to conducting foreign inspections, but specific implementation steps and associated time frames are unclear. We previously identified the lack of a dedicated staff devoted to conducting foreign inspections as a challenge for the agency. FDA noted in its report on the revitalization of ORA that it is exploring the creation of a cadre of investigators who would be dedicated to conducting foreign inspections.[33] However, the report does not provide any additional details or timeframes about this proposal. In addition, FDA recently announced plans to establish a permanent foreign presence overseas, although little information about these plans is available. Through an initiative known as "Beyond our Borders," FDA intends that its foreign offices will improve cooperation and information exchange with foreign regulatory bodies, improve procedures for expanded inspections, allow it to inspect facilities quickly in an emergency, and facilitate work with private and government agencies to assure standards for quality. FDA's proposed foreign offices are intended to expand the agency's capacity for regulating, among other things, drugs, medical devices, and food. The extent to which the activities conducted by foreign offices are relevant to FDA's foreign drug inspection program is

[32]FDA also proposed a reinspection user fee in its fiscal year 2007 and fiscal year 2008 budgets, but these proposals were not enacted.

[33]See, for example, Food and Drug Administration, *Revitalizing ORA: Protecting the Public Health Together In a Changing World* (Rockville, Md.: Jan. 2008).

uncertain. Initially, FDA plans to establish a foreign office in China with three locations—Beijing, Shanghai, and Guangzhou—comprised of a total of eight FDA employees and five Chinese nationals. The Beijing office, which the agency expects will be partially staffed by the end of 2008, will be responsible for coordination between FDA and the Chinese regulatory agencies. FDA staff located in Shanghai and Guangzhou, who will be hired in 2009, will be focused on conducting inspections and working with Chinese inspectors to provide training as necessary. FDA has noted that the Chinese nationals will primarily provide support to FDA staff including translation and interpretation. The agency is also considering setting up offices in other locations, such as India, the Middle East, Latin America, and Europe, but no dates have been specified. While the establishment of both a foreign inspection cadre and offices overseas have the potential for improving FDA's oversight of foreign establishments and providing the agency with better data on foreign establishments, it is too early to tell whether these steps will be effective or will increase the number of foreign drug inspections.

Agreements with foreign governments, such as one recently reached with China's State Food and Drug Administration, may help the agency address certain logistical issues unique to conducting inspections of foreign establishments. We previously testified that one challenge faced by FDA involved the need for its staff to obtain a visa or letter of invitation to enter a foreign country to conduct an inspection. However, FDA officials told us that their agreement with China recently helped FDA expedite this process when it learned of the adverse events associated with a Chinese heparin manufacturer. According to these officials, the agreement with China greatly facilitated its inspection of this manufacturer by helping FDA send investigators much more quickly than was previously possible.

## Concluding Observations

Americans depend on FDA to ensure the safety and effectiveness of the drugs they take. The recent incident involving heparin underscores the importance of FDA's initiatives and its steps to obtain more information about foreign drug establishments, conduct more inspections overseas, and improve its overall management of its foreign drug inspection program. FDA has identified actions that, if fully implemented, could address some, but not all, of the concerns we first identified 10 years ago and reiterated 5 months ago in our testimony before this subcommittee. Given the growth in foreign drug manufacturing for the U.S. market and the current large gaps in FDA's foreign drug inspections, FDA will need to devote considerable resources to this area if it is to increase the rate of inspections. However, FDA's plans currently call for incremental increases

that will have little impact in the near future to reduce the interval between inspections for these establishments. In addition, many of FDA's initiatives will take several years to implement and require funding and certain interagency or intergovernmental agreements that are not yet in place. Taken together, FDA's plans represent a step forward in filling the large gaps in FDA's foreign drug inspection program, but do little to accomplish short-term change.

Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or the other Members of the subcommittee may have at this time.

## Contacts and Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. Geraldine Redican-Bigott, Assistant Director; Katherine Clark; William Hadley; Cathleen Hamann; Julian Klazkin; Lisa Motley; Daniel Ries; and Monique B. Williams made key contributions to this testimony.

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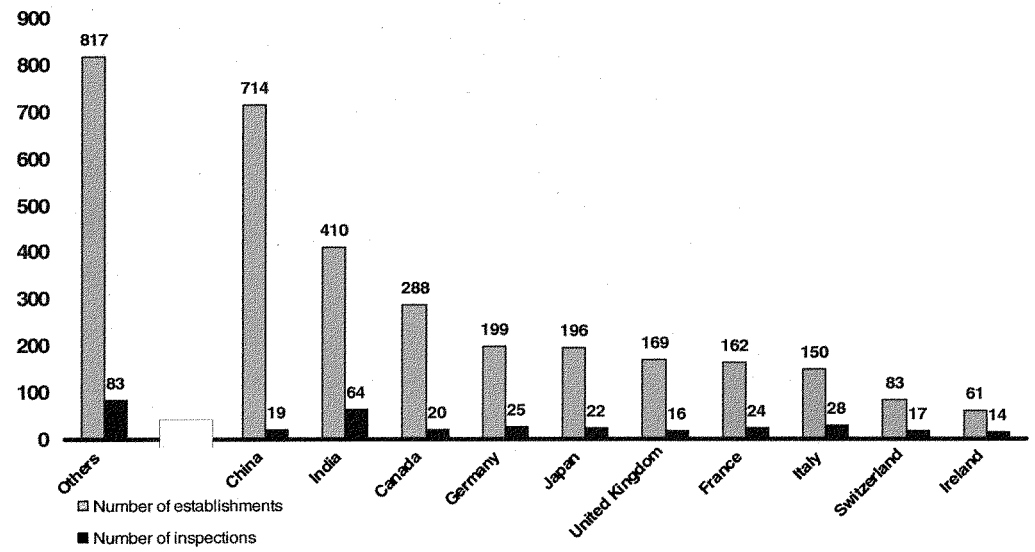
# Number of Foreign Establishments and FDA Inspections, including for the 10 Most Frequently Inspected Countries, Fiscal Year 2007




Source: GAO analysis of FDA data.

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# Examples of manufacturer information and MIDs:

**LA VIE DE FRANCE**
243 Rue de la Payees
62591 Bremond, France
Order Date:
Item Number:
Quantity:
Destination:

**MID: FRLAVIE243BRE**

**20TH CENTURY TECHNOLOGIES**
5 Ricardo Munoz, Suite 5880
Caracas, Venezuala
Order Date:
Item Number:
Quantity:
Destination:

**MID: VE20TCEN5880CAR**

**N. MINAMI & CO.,LTD.**
2-6, 8-Chome Isogami-Dori,Fukiai-Ku
Kobe, Japan
Order Date:
Item Number:
Quantity:
Destination:

**MID: JPMINCO268KOB**

| | | | |
|---|---|---|---|
| **FR** | **VE** | **JP** | The ISO country code |
| **LA VIE** | **20T CEN** | **MIN CO** | The first three letters of the first and the first three letters of the second name of the manufacturer |
| **243** | **5880** | **268** | Up to four numbers from the manufacturer's address, if there are numbers in the address line. Brokers find the largest number on the address line and use up to the first four digits (e.g. If the address is 11455 Main Street Suite 9999, the customs broker would enter "1145" for this section of the MID). |
| **BRE** | **CAR** | **KOB** | The first three letters of the city in which the manufacturer is located |

Source: GAO analysis of Customs and Border Protection information.

Mr. STUPAK. Thank you, Doctor.
Dr. Cassell.

**STATEMENT OF GAIL H. CASSELL, PH.D., VICE PRESIDENT, SCIENTIFIC AFFAIRS AND DISTINGUISHED LILLY RESEARCH SCHOLAR FOR INFECTIOUS DISEASES, ELI LILLY AND COMPANY**

Dr. CASSELL. Mr. Chairman, members of the subcommittee, I am Gail Cassell, Vice President for Scientific Affairs and Distinguished Research Scholar for Infectious Diseases at Eli Lilly and Company. Of relevance to my testimony today, I have previously been a member of the advisory committees of the Directors of both Centers for Disease Control and the National Institutes of Health. And in 1994–95 I also cochaired the congressionally mandated review of the NIH Intramural Program. I appear before you today as a member of the FDA Science Board, Advisory Committee to the FDA Commissioner. I served as Chair of the Subcommittee on Science and Technology of the Science Board, which authored the report that you have heard referenced today by Chairman Stupak, the "FDA Science and Mission At Risk."

By way of background I just remind you that in December of 2006, the Commissioner charged the Science Board with establishing a subcommittee to assess whether or not FDA's current science and technology can support the Agency's statutory mandate to protect the Nation's food and drug supply. You have already also heard Mr. Stupak allude to the composition of the Committee. I would just emphasize that this committee was made up of a very distinguished group of 30 experts, including former deputy—our former Chief Counsel to the FDA, as well as knowledgeable experts, some of whom had worked in FDA. Over 14 members of the 30—of the 33-member committee were members of the National Academy of Sciences, and we had one Nobel laureate.

The record of the proceedings of the meeting in which we presented the results of this report will show that the full report was accepted by the full Science Board and, in fact, the full 33-member committee adopted the recommendations of the report.

For over a year this group of experts worked intensively conducting their review. It became rapidly apparent that the FDA suffers from serious scientific deficiencies and is not in a position to meet current or emerging regulatory responsibilities. It is agency-wide and not limited to a single program or center. Since every regulatory decision must be based upon the best available scientific evidence in order to protect the public's health, we concluded that American lives are at risk and that there is an urgent need to address these deficiencies.

Of relevance to the topic that we have at hand today, which is that of foreign inspections, especially for drugs, I might add that many aspects of food and drug manufacturing also should be based upon the latest, very latest science and technology, including scientific methods and technologies that are the latest as far as specificity and sensitivity for detecting not only chemical contaminants but also microbial contaminants, and that we should have investigators in the field performing those manufacturing inspections

that in fact are qualified in terms of quality control and scientific expertise.

The level of concern by all of the members of our subcommittee of the Science Board was and remains high, and thus the intensity of our commitment to the review and their insistence that define our findings be broadly communicated. Quite simply, what we found is that FDA resources have not increased, while the responsibilities have increased extraordinarily, and you have heard that from many different individuals today and you'll hear further from others.

We also found that the Agency has not adapted in order to maximize existing resources by capitalizing upon scientific resources in the academic community and other government agencies; i.e., leveraging their resources. The specifics of our finding was the subject of a hearing, as you have heard Mr. Stupak refer to this morning, on January the 29th. So I will not discuss all the findings in detail, but I would rather like to focus upon those aspects of our review that are most relevant to the topic of today's hearing on foreign inspection.

Number one is the area of growing disparity between responsibility and resources; two, gaps in scientific capacity and capability, information technology and to a lesser extent organizational structure.

With regards to growing disparity between FDA responsibility and resources, there is no more quintessential governmental responsibility than the protection of basic commodities of American life, such as our food and drugs. The Science Board emphasizes that the need for an effective FDA is greater today than ever before since the FDA regulates 80 percent of the Nation's food supply, plays a critical role in assuring the safety of therapeutics and vaccines and devices, and regulates a vast number of other consumer products, and historically has been the Agency to which governments around the world look to for determinants of the safety of products.

Moreover, something that hasn't been mentioned today, I would like to emphasize that FDA is increasingly important to the Nation's economic health, as it regulates a quarter of consumer expenditures, and the industries that it regulates are innovative leaders in science and technology and among the few American industries with a positive trade balance with other nations. Further, FDA will be a critical component in combating bioterrorism. That has been alluded to this morning but not to any great extent. It is something that certainly should be of great concern to all of us as we talk about potential for intentional contamination of the food and drug supply as it relates to bioterrorism.

The Science Board concluded that FDA is slowly being hollowed out by a progression of budget cuts and inattention to the Agency's needs. That deterioration in turn means that not only can the Agency not fulfill its public health mission, but that the safety of the citizens and the well-being of our country are undermined. Furthermore, as the Agency falls further and further behind, the public is increasingly losing confidence in the government's ability to protect them.

The demands upon the FDA have soared. As we have already said, the metrics alone are daunting, 125 new statutes added to the FDA's workload by Congress in the past two decades, most without resources. And in reference to the number of establishments we were told during our review that there were a total of 375,000 establishments outside the United States making products coming into the United States and in effect that these were on all continents and over 100 countries.

In addition, there has been a tripling in a decade of R&D and drugs and medical devices; an exponential increase in drug adverse reaction reports and the emergence of extraordinarily new health threats that threaten contamination of products, including mad cow disease, E. coli 157, et cetera.

But perhaps most emblematic of the trend is the tenfold increase in the past decade of imports from other countries. Today, as you know, 15 percent of our food supply is imported from more than 100 nations, along with over half the drugs. Yet FDA has been given virtually no new authorities nor resources to address such a dramatic change in the sourcing from products made overseas often in developing countries with little or no tradition of scientific rigor.

What about gaps in capacity and expertise? FDA's resources have not only not kept pace with responsibilities, many critical agency programs have sustained actual cuts. I won't go into the cuts as it relates to food, but certainly that was one of our areas of biggest concern.

Although one FDA function, new drug and device review, has received additional funding from industry paid user fees, it is important for you to realize that the Agency as a whole has lost a thousand people over the past decade that perform critical function. Some of them relate to, of course, the foreign inspection that we are talking about today. This loss in scientific capacity has resulted in loss of personnel to perform not only the inspection associated with marketed products, but is equally important in that it has resulted in loss of individuals in critical areas of scientific expertise, and we will come back to that in a minute.

Innovations and advancements in science are outstripping FDA's capacity to understand and regulate them, and I would contend that this applies both with regards to manufacturing of those new products as much as it does to pre-approval of those new products.

We are on the cusp of another revolution in therapeutics, breakthroughs in human, animal, and microbial genomics, molecular biology, nanotechnology, computational mathematics, imaging, et cetera, that will revolutionize not only medicine and food production, but also drugs for animal health. Yet FDA is not and does not have the capacity to prepare for these breakthroughs, whether it be again in the pre-approval process or the post-marketing surveillance or manufacturing inspection.

Tens of billions of dollars are being spent by both the public and private sector on the development of such products, yet FDA has been denied the relatively minor funding necessary to ensure their rapid and safe entry into the market. At a time in which U.S. competitors in science, medicine and food production are under increasing strain from overseas, a weak and underfunded FDA will be a

brake on the very technologies that the United States is relying on for its medical and technological future.

It is absolutely critical that individuals involved in inspection of these products coming in from overseas in terms of manufacturing inspections have the adequate science and technology to allow them to do a better job than they are currently able to do today. They should have the methods to perform increased sensitivity tests in looking for contaminants, both chemical and microbial, both in drugs and in vaccines, biologics, and also food, perhaps even including, something, as we heard this morning, maybe others would not call it quite as sophisticated, it is much more practical than most would admit, but perhaps information technology as well.

I would also be remiss if I did not remind you, however, that again the FDA's food safety program is one that needs the greatest support with regards to these new technologies because they are simply at rock bottom, both in terms of numbers of scientists but also their scientific capabilities as far as monitoring the food supply.

The Science Board subcommittee viewed the current scientific needs of FDA to be extensive and diverse in critical terms—in terms of critical expertise, infrastructure and knowledge perhaps, as I have said, across the Agency, and we do believe that this is a serious impediment.

FDA, in terms of the recent heparin episode, illustrates just how critical science is at FDA for monitoring of drug quality. We heard during our review of the Center for Biologics, for example, that that center mandates that some of their scientists be present in manufacturing inspections to play a role in quality control; i.e., so that they can be assured that the right technologies are being applied to evaluate the quality of the drugs being manufactured, and I would submit to you that this should be something that shouldn't be an exception with regards to biological products or vaccines, but it also should be true for drugs.

It is commendable that FDA was able to develop a new test very quickly that has picked up the contaminant in heparin, but also has certainly shared it around the world, but in fact perhaps it could have been done more quickly had more sensitive tests been in operation and in use all along.

Mr. STUPAK. Doctor, would you summarize?

Dr. CASSELL. Yes, thank you.

In conclusion, FDA can no longer fulfill its mission without substantial and sustained additional appropriations, particularly in the area of information technology. Others will address this in detail. I will in the questioning if asked. The current situation has developed over years. The question is not why or how we got here but how we are going to go forward.

The report actually, we would argue, would serve as a blueprint with regards to that and we recognize that financial additions to the budget are not the only answer, as we already heard this morning. While our report focused upon the FDA organizational structure related most to the scientific infrastructure, it might well be in light of continuing issues related to globalization that we should be asking what FDA organizational structure is needed to protect the public's health in the 21st century setting of globalization with

rapidly expanding importation of foreign drugs, vaccines, and biologics. And again, while our subcommittee focused on organizational structures that related to the scientific infrastructure, Congress may like to consider requesting, for example, the Institute of Medicine to perform a more in-depth study to evaluate overall agency structure as it relates to food safety and also drug safety.

And with that, because I am out of time I will stop, but thank you very much for your patience.

[The prepared statement of Ms. Cassell follows:]

## STATEMENT OF GAIL H. CASSELL, PH.D.

Mr. Chairman and Members of the Subcommittee, I am Gail H. Cassell, Vice President for Scientific Affairs and a Distinguished Research Scholar for Infectious Diseases of Eli Lilly and Company. I am also Professor and Chairman Emeritus of the Department of Microbiology of the University of Alabama Schools of Medicine and Dentistry. I am a member of the Institute of Medicine of the National Academy of Sciences and am currently serving a second term on the governing board of the IOM. Of relevance to my testimony today, I have previously been a member of the Advisory Committees of the Directors of both the Centers for Disease Control and the National Institutes of Health (NIH). In 1994–95, I also co-chaired the congressionally mandated review of the NIH intramural program. I appear before you today as a member of the FDA Science Board, Advisory Committee to the FDA Commissioner. I served as Chair of the Subcommittee on Science and Technology of the Science Board, which authored the report "FDA Science and Mission at Risk."

### BACKGROUND

In December 2006, the Commissioner charged the Science Board with establishing a subcommittee to assess whether FDA's current science and technology can support the Agency's statutory mandate to protect the Nation's food and drug supply. The subcommittee was comprised of three Science Board members and 30 other experts. The subcommittee formally presented its report to the Science Board and FDA on December 3, 2007. The report was unanimously endorsed by each of the 33 members of the Subcommittee and the full Science Board. The Science Board accepted the report as final and dissolved the subcommittee. The record of the proceedings of that meeting will show that due to the seriousness of the deficiencies found and the urgency of the situation, the Science Board was adamant that the report be broadly disseminated among the public and policy makers, including posting it in the Federal Register.

The subcommittee review was unique in many respects. First, it is only the second time in over a century that the Agency has been reviewed by an external committee reviewing the Agency as a whole entity. Second, the Committee was composed of leaders, not from a single sector, but from industry, academia, and other government agencies. The expertise and level of accomplishments of the members are almost unprecedented in a single committee, especially considering their breadth and knowledge in regulatory science and understanding of the mission of the Agency.

The subcommittee included expertise ranging from a Nobel laureate in pharmacology, 14 members of the National Academy of sciences (including two engineers), a renowned economist and specialist in workforce issues, a leader in health care policy and technology assessment, a former CEO of a large pharmaceutical company, a former Assistant Secretary for Health and Human Services who also headed global regulatory affairs within a large company for over 20 years, a former Chief Counsel for the FDA, and the first under Secretary for Food Safety at the U.S. Department of Agriculture overseeing the Food Safety and Inspection Service and coordinating U.S. government food safety policy.

For over a year, this group of experts worked intensively conducting their review. It became rapidly apparent that the FDA suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities. It is agency wide, i.e. not limited to a single program or Center. Since every regulatory decision must be based upon the best available scientific evidence in order to protect the public's health, we concluded that American lives are at risk and that there is an urgent need to address the deficiencies. The level of concern by all members of the Subcommittee and the Science Board members was, and remains, high, and thus the intensity of their commitment to this review and their insistence that the findings be broadly communicated.

What we found is, quite simply, demands of FDA have soared over the past two decades. Resources have not! Furthermore, we found that the Agency has not adapted in order to maximize existing resources by capitalizing upon the scientific resources in the academic community and other government agencies.

The specific findings of our review were the subject of a hearing of this Oversight Committee held on January 29, 2008 "Science and Mission at Risk: FDA's Self-Assessment." Thus, I will not discuss all of the findings in detail today but rather I would like to focus upon those aspects of our review that are most relevant to the topic of today's hearing on foreign inspections: 1) Growing Disparity Between Responsibilities and Resources; 2) Gaps in Scientific Capacity and Capability; 3) Information Technology; and 4) Organizational Structure.

### GROWING DISPARITY BETWEEN FDA RESPONSIBILITIES AND RESOURCES

There is no more quintessential governmental responsibility than the protection of basic commodities of American life such as our foods and drugs. The Science Board report emphasizes that the need for an effective FDA is greater than ever before: FDA regulates 80% of the nation's food supply; plays a critical role in assuring the safety of therapeutics such as drugs, vaccines, and medical devices; regulates a vast number of other consumer products, ranging from televisions and cellular telephones to cosmetics, blood, and pet food; and has historically been the Agency to which governments around the world look to make determinations about the safety of new products. Moreover, the FDA is increasingly important to the Nation's economic health, as it regulates a quarter of consumer expenditures, and the industries it regulates are innovative leaders in science and technology and among the few American industries with a positive trade balance with other nations. Further, FDA will be a critical component in combating emerging threats such as intentional contamination of the food supply and the threat of chemical, biological and radiological attack-as well as naturally occurring threats such as SARS, West Nile virus, and avian influenza.

The Science Board concluded that FDA is being slowly "hollowed out" by a progression of budget cuts and inattention to the Agency's needs. That deterioration, in turn, means that not only can the Agency not fulfill its public health mission, but that the safety of our citizens and the well being of our economy are being undermined. Further, as the Agency falls farther and farther behind, the public is increasingly losing confidence in the government's ability to protect them.

The demands upon the FDA have soared due to the extraordinary advance of scientific discoveries, the complexity of the new products and claims submitted to FDA for approval, the emergence of heretofore unknown health threats, and the globalization of the industries that FDA regulates. The metrics alone are daunting, 125 new statutes added to FDA's workload by Congress in the past two decades, most without resources to implement them; 375,000 establishments making FDA-regulated products; a tripling in a decade of R & D in drugs and medical devices; an exponential increase in drug adverse reaction reports; and the emergence in recent years of extraordinary new health threats, such as, E. coli 0157H:7, AIDS, mad cow disease, and more. Perhaps most emblematic of this trend is the ten fold increase in the past decade of imports from other countries. Today, 15% of our food supply is imported from more than 100 nations, along with over half of our drugs, yet FDA has been given virtually no new authorities nor resources to address a dramatic change in the sourcing (and associated risk) from products made overseas, often in developing countries with little or no tradition of scientific rigor.

### GAPS IN SCIENTIFIC CAPACITY AND EXPERTISE

FDA's resources have not only not kept pace with its responsibilities, many critical agency programs have sustained actual cuts. For example, FDA's food headquarters program has lost 20% of its scientists in just the past three years, despite an upswing in outbreaks of foodborne disease in the United States and a steady increase in contaminated seafood, produce and other foods being imported from foreign countries. Similarly, FDA has lost several hundred inspectors due to budget cuts since 2003, leaving the Agency not only incapable of inspecting domestic manufacturers but also ensuring that most of the nation's ports have no FDA inspectors. Although one FDA function, new drug and device review, has received additional funding from industry-paid user fees, the Agency as a whole has lost 1000 people over the past decade. This loss in scientific capacity has resulted in loss of personnel to perform inspections associated with marketed products but equally important, it has resulted in significant and critical gaps in scientific expertise.

Innovations and advancements in science are outstripping FDA's capacity to understand and regulate them, threatening not only the safe introduction of new tech-

nologies but also American leadership in pharmaceuticals, vaccines, biotechnology, and medical devices. The United States is on the cusp of another "revolution" in therapeutics that holds great promise for effective treatments of cancer, Alzheimer's, Parkinson's, and other previously incurable conditions. Breakthroughs in human, animal, and microbial genomics, molecular biology, nanotechnology, food processing technology, computational mathematics, in vivo imaging and many more are likely to change the face of medicine and food production, yet FDA has not been given the capacity to prepare for these breakthroughs. Tens of billions of dollars are being spent by both the public and private sector on the development of such products, yet FDA has been denied the relatively minor funding necessary to ensure their rapid and safe entry into the market. At a time in which U.S. competitiveness in science, medicine, and food production are under increasing strain from overseas, a weak and underfunded FDA will be a brake on the very technologies that the United States is relying upon for its medical and technological future.

Our Science Board Subcommittee considered the funding issues to be more acute for the Center for Food Safety and Applied Nutrition (CFSAN) than for other FDA programs. FDA's food safety program is characterized as one steadily dropping in staffing, and in funding for essential functions. Budget cuts for food safety have brought the Agency from doing 35,000 domestic food inspections in 1973 to fewer than 8000 in 2007 (meaning FDA inspects most facilities on average only every 10 years). The foreign inspection rate is even worse, as the Agency may manage to inspect a dozen foreign food manufacturers in 2008, despite the thousands of overseas producers sending food to our shores. Moreover, as FDA's leadership in food safety erodes, other countries are presenting themselves as the appropriate model for food safety standard setting, even though such standards can be unscientific and disguised trade barriers, to the detriment of principles of sound science and to market access for American food exports. A recent GAO report indicates that less than 7% of foreign drug manufacturing sites are inspected annually be FDA.

The Science Board Subcommittee viewed the current scientific needs of FDA to be extensive and diverse in terms of critical expertise, infrastructure, and knowledge gaps across FDA. Again, they were particularly critical in CFSAN. The food industry is rapidly changing both in terms of its global nature and the sophistication of the technologies used for production, processing, and marketing. In addition, the hazards related to food are changing and evolving in concert with changing food technologies and food production locales. The food regulatory program lacks sufficient high-quality applied field and laboratory research data to understand the mechanisms of contamination and how to mitigate or eradicate the many pathogens involved in the food production process. Additionally, CFSAN scientists are limited in their knowledge of food production, whether in the agricultural or aquacultural aspects of food production, especially in foreign production arenas. The capability and capacity of FDA to detect food-borne viruses and parasites have not kept pace with the emergence of this public health threat from international sources. It is essential that FDA have the capability to rapidly detect food-borne pathogens. Currently they are limited in scope and have lengthy time requirements. Quick high throughput technologies are needed. This is a serious impediment to the US food safety program. Likewise, quick high throughput technologies are needed for detecting chemical contamination in both food and drugs. While the FDA was able to develop an assay for screening of heparin during the recent adverse reactions, the assay needs to be adapted to high throughput with improved sensitivity and adoption for field use.

### Information Technology Systems

FDA's information technology systems are woefully outdated and inadequate, posing a concrete threat to the Agency's public health mission. The report's authors were extremely disturbed by the state of FDA's IT infrastructure. We found a situation problematic at best, at worst dangerous. Many of FDA's systems are far beyond their expected life span, and systems fail frequently (even email systems are unstable). Emergency back-up systems are not in place. I heard recently that the newly established program related to adverse event reporting was lost due to failure of a back-up system. This has already resulted in a 6 week delay in implementation and it remains inoperable. Reports of product dangers are not rapidly compared and analyzed, inspectors' reports are still laboriously handwritten, and the system for managing imported products cannot communicate with Customs and other government systems. These inadequacies do not only cause inefficiencies and waste, but more importantly mean that dangers lurking in information coming to the FDA are simply missed—such as drug adverse reactions that are duly reported but not flagged for attention due to incapacities in information management. Data bases

and data mining capabilities for appropriate tracking of inspections sites has proved to be a major challenge with existing technology and expertise. Inaccurate data bases and data bases not easily mined continue to hamper foreign inspections for drug manufacturing even though some of the problems were identified by GAO over a decade ago.

CONCLUSION

FDA can no longer fulfill its mission without substantial and sustained additional appropriations. The current situation has developed over many years, the question is not why or how we got here but rather how do we strengthen FDA going forward? Our subcommittee strongly believes our report provides the required blueprint.

The report is unique in yet another important way. It not only provides an assessment by a rigorous review of the Agency by a diverse team of experts from the public and private sectors, but it also includes a simultaneous assessment by leaders of the FDA (as contained in Appendices L–M). Our Subcommittee requested staff to not only identify science and technology gaps but to link each directly to their specific regulatory mission. This comprehensive external/internal analysis—done at the same point in time for an entire Agency—is indeed rare.

We recognize that adequate resources—human and financial—alone will not be sufficient to repair the deteriorating state of science at FDA, which is why our committee also recommended significant restructuring. While our report focused upon the FDA organizational structure related most to the scientific infrastructure, it might well be that in light of continuing issues related to globalization that we should be asking "What FDA organizational structure is needed to protect the public's health in the 21st century setting of globalization with rapidly expanding importation of foreign drugs, vaccines, biologics, and food?" While our Subcommittee recommended that the Science Board conduct an extensive review of the Office of Regulatory Affairs and the National Center for Toxicological Research, Congress may want to consider requesting IOM to perform a more in depth study to evaluate the overall Agency structure given the concerns also raised regarding structure and drug safety. Regardless of the organizational structure, it is clear that without a substantial increase in resources, the Agency will be unable to meet either the mandates of Congress or the expectations of the American public, regardless of management or leadership changes. Our findings are supported by many recent GAO reports as you will hear today as well as recent reports form the congressional Research Service and the National Academy of Sciences.

On behalf of our Subcommittee, we thank Chairmen Stupak and Dingell and ranking members Barton and Shimkus for holding this hearing and for your recognition of the seriousness of the deficiencies we have identified and the urgency with which they need to be addressed. The urgency of our advisory is simply predicated upon the fact that we see signs of an increasingly chaotic environment descending upon FDA, and the need to address the deficiencies we identified. Without immediate action, injuries and deaths from an overwhelmed regulatory system are certain, and the costs to our society will be far greater than any dollar figure upon which we all can agree.

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Mr. STUPAK. Thank you, Doctor.

Mr. Hubbard, please, for your opening statement.

## STATEMENT OF WILLIAM K. HUBBARD, FORMER FDA ASSOCIATE COMMISSIONER AND CURRENT SENIOR ADVISOR TO THE COALITION FOR A STRONGER FDA

Mr. HUBBARD. Thank you, Mr. Chairman. I have written testimony. I will just make a few opening remarks.

It is ironic but sad that we were here on November 1st talking about this at the very time when the initial heparin deaths began to come in in reports, and so I appreciate the fact that you stayed with this issue because I do think it needs to be stayed with until we find a solution. And while FDA can't with absolute certainty associate the contamination from Chinese sources, the evidence is pretty darn strong, and the inadequate conditions that the FDA

found when it did inspect the facility in Changzhou is, I think, indisputable.

I can't overemphasize the risk we are putting our citizens through by continuing to allow these products to come into our country with no FDA screening.

You referred, Mr. Chairman, in your opening remarks to Commissioner Cassell's remarks about why the FDA was created. I think that is a very appropriate analogy for us to consider. When Congress created the FDA in '06 you had a marketplace overrun with problems with foods and drugs, and there were three characteristics. You had widespread substitution of cheap, but unsafe food and drug ingredients, things like talcum for flour and sawdust for cereal, an abundant use of all kinds of chemicals and drugs and products driven more by profit motive than by quality, and lastly a weak-to-nonexistent regulatory system. Well, you know, that sounds familiar, doesn't it? So these factors are very clearly the case now with our import system.

FDA has found substitutions of cheaper but dangerous ingredients, and that is often from less developed nations. You had mentioned melamine, the antibiotics in seafood, saccharine masking putrid fish, watered-down apple juice. The list is a fairly long one. And further, foreign producers, as you referred earlier, Mr. Chairman, can rely on the fact that FDA is not on the case and that a firm is unlikely to be caught and then if they are caught they are unlikely to be punished, and so that the incentives are all in the wrong place.

And then—and then lastly, you have got equally evident that the governments of these nations are incapable, in my view, of assuring the safety of the products they send to us. In fact, they often deny the very existence of the problem. So we really only have three alternatives. We do nothing, that has just been the default for many years, and just hope for the best. We can rely on the assurances of these foreign governments, but as I said, I just don't think that is meaningful in this environment. Or we can accept the fact that we have not taken care of the FDA and given it the means.

So I'll note that we have built a terrific regulatory authority in this country with over almost a century. We have built up the FDA, it has wonderful scientists and dedicated personnel, but we don't use it in protecting us from these foreign drugs, which I just think is a tremendous lapse. And we have not given them the tools and resources they need. You know as consumers we spend a penny and a half a day on the FDA. And I believe if we just spend 2 or 3 cents a day on the FDA that we could fix these problems.

And I think if you polled American citizens, they would put FDA—the things that FDA does—at the top five or six things that they would want to see their tax funds spent for. And if we don't do something, Mr. Chairman, I think we are going to be back here over and over again having these same discussions. And in fact, these foreign drugs form a string of ticking time bombs. Heparin's gone off and I think there are going to be more until we fix this problem.

And so with that, I thank you for your time.

[The prepared statement of Mr. Hubbard follows:]

## STATEMENT OF WILLIAM K. HUBBARD

### INTRODUCTION

Mr. Chairman and members of the Committee, I am William K. Hubbard. Before my retirement after 33 years of Federal service, I served for many years with the U.S. Food and Drug Administration, and for my last 14 years was an FDA Associate Commissioner responsible for, among other things, FDA's regulations and policy development. Although I remain retired since my departure from FDA, I serve as an advisor to The Alliance for a Stronger FDA, a consortium of patient, public interest, and industry organizations whose mission is to urge that FDA's appropriations be increased. The Alliance and its constituent members are greatly concerned that FDA's resource limitations have hampered the Agency's ability to ensure the safety of our food and drug supply. Today's hearing is a further exploration of your recent focus on one of those concerns—the massive increase in pharmaceuticals being imported into the United States at a time in which FDA's capacity to oversee those foreign producers is in serious doubt. Accordingly, I wish to thank the Committee for inviting me to testify on that subject today.

### BACKGROUND

As you know, Congress created the current regulatory structure for assuring the safety of human drugs in 1938, through its enactment of the Food, Drug and Cosmetic Act. That statute recognized that drugs could be a key component of our health care system, but that drugs were also powerful chemicals with the capability to produce great harm if not carefully regulated. Thus, Congress determined it necessary to create a relatively pervasive regulatory system, a key part of which is oversight of the production processes by which our drugs are manufactured. In carrying out its congressional mandate, FDA has promulgated regulations that provide specific requirements for drug manufacturers to meet, known as GMPs (for Good Manufacturing Practices). These include requirements that active ingredients of the drug be of a prescribed purity, strength and quality; that the drug be made in well controlled, sanitary conditions; that its labeling and packaging be equally well controlled; and that laboratory tests of the drug be performed routinely using well established scientific methods and properly calibrated equipment to confirm that the drug is always produced in the form approved by the FDA.

GMPs and Domestic Drug Production—A Successful Safety Record. The result of this regime, established by Congress, and implemented by FDA and drug manufacturers, has been a domestic drug supply in which Americans can have great confidence with regard to quality and safety. Combined with the success of the user fee program that this committee created, we have access to new drugs as fast or faster than anywhere else in the world and we can be assured that our medications produced in the United States conform to equally high production standards. Moreover, countries around the world have been able to look to the FDA as the "gold standard" for determining if a new drug should be approved and for establishing safe manufacturing controls for marketed drugs. But the investigations you have been pursuing in recent months with regard to imported drugs point to a dark side of drug manufacturing that threatens to undercut the hard work of so many and the traditional safety assurances upon which we have long relied.

### FOREIGN SOURCING OF THE U.S. DRUG SUPPLY

The reason for this concern, of course, is that 80% of the active ingredients in our drugs are now coming from overseas, and increasingly the so-called "finished pharmaceutical"—the pill we take by mouth or liquid injected into our bodies—is being produced in other countries as well. Further, the most rapid growth in foreign drug suppliers has occurred in developing nations such as China and India, with the prospect of future suppliers from Vietnam, Thailand, Malaysia, and a host of African counties. Unfortunately, we know from experience that drugs produced overseas are not given the same "special" treatment that we have given drugs made here in the United States. In most countries, pharmaceuticals products are subject to normal arbitrage, which means that drugs move about much as do electronics, apparel, auto parts and thousands of other goods. This has meant that drugs are often purchased from suppliers who have little or no oversight by regulatory bodies; that key elements of safe drug production are ignored—such as quality testing, expiration dating, and labeling; and that producers of substandard and counterfeit drugs have a relatively easy access to the marketplace. Finally, in less developed countries, it is abundantly clear that the regulatory bodies, if they exist at all, are weak and ill

prepared to assure the safe production, distribution, and storage of drugs being exported to the United States.

## DRUG COUNTERFEITING

Further complicating and endangering this situation is the prevalence of counterfeiting around the world. We, of course, see counterfeit designer clothing, watches and videos being sold on street corners across the country. But a fake Gucci bag is likely to pose little threat to your health, while counterfeit drugs are reported to cause deaths in the hundreds of thousand worldwide each year. In some countries, it is estimated that a patient is more likely to get a counterfeit drug than a real one, meaning that more than half of that nation's drug supply is fake. Indeed, drug counterfeiting is considered to be endemic around the world, with the United States, until recently, a rare exception. But that may be changing rapidly. FDA has seen its counterfeit drug caseload soar in recent years, paralleling the movement of drug production from domestic to foreign sources.

Perhaps this is coincidental, but certainly China has been alleged to be a principle world supplier of counterfeit products. For example, a "sting" operation by the The Sunday Times of London last year set up a phony drug wholesaler, who was able to buy large quantities of counterfeit drugs from a Chinese manufacturer, who was reported to make pharmaceutical ingredients for legal sale by day and fake drugs for illicit sale by night. The Times reported that counterfeiters are increasingly turning from fake handbags and currency to drugs, because the drugs are so easy to make and sell on world markets.

And the New York Times described recently how counterfeit glycerin, which has been linked to hundreds of deaths in children when used in cough syrups and analgesics, was traced through a pipeline "from the Panamanian port of Colon, back through trading companies in Barcelona, Spain, and Beijing, to its beginning near the Yangtze Delta in a place local people call 'chemical country'."

## FDA AND IMPORTED DRUGS

As this is occurring, what has been the reaction by our regulatory structure—the FDA? I recognize that you and others in Congress have been highly critical of FDA's oversight of drug imports in a number of areas—poor identification of foreign drug sourcing, little examination or testing of drugs when they arrive at U.S. ports, and virtually no routine surveillance of foreign drug manufacturers for adherence to GMPs. But, as you know, I have often defended the Agency as a cadre of highly capable, dedicated public servants who are struggling to keep up with the challenges of a rapidly changing pharmaceutical supply chain. I contend that we as a nation have failed to give FDA the tools it needs to carry out the mission we have assigned to them, such as:

- Staff to conduct regular inspections in foreign facilities as are now done for domestic manufacturing plants;
- Modern IT systems that would allow FDA to effectively track and monitor the production and movement of imports. The import data system is so old and communicates so poorly with other FDA information systems that it is difficult for FDA officials to use risk as a predominant driver of their compliance;
- Registration procedures for foreign drug manufacturing that would allow us to know who is making drugs for our market, where they are located, and what they are manufacturing; and
- Port inspectors to examine the almost 20 million annual shipments of foods, drugs, and other products that FDA is expected to regulation. For over 400 ports of entry, FDA has only 450 inspectors, meaning that most ports aren't staffed at all and many can be staffed only part time.

Irrespective of particular needs, however, we must also face up to the fact that FDA is asked to regulate these products with a law whose 70th anniversary is this year—a time in which there were few drugs being made anywhere in the world, and none being imported into the United States. To use a transportation analogy, drug manufacturing has moved in the ensuing years from automobiles to airplanes to spacecraft, and FDA is still driving a Ford Model T, at least with respect to imported drugs. Current law and resource allocations for the FDA place most of the responsibility for assuring the safety of imported drugs on the Agency. So, while domestic drug manufacturers are held to a high standard of drug safety, with regular GMP inspections, foreign producers often need worry only about the remote possibility that an FDA inspector at a border crossing will find a problem and stop the drug's entry.

WHERE DO WE GO FROM HERE?

I recognize that members of Congress on both sides of Capitol Hill are considering a number of legislative improvements to address import safety. Making major changes in the regulatory structure will likely be akin to turning a giant oil tanker—you can start the turn now, but it will take considerable time to fully change direction. But I believe there are some key principles that could be adopted right away, which have been suggested by the GAO and by FDA's Science Board:

1) **We need to initiate GMP inspections of foreign drug manufacturing facilities immediately, with a special focus on drugs made in countries without a safe drug production and internal regulation.** Without such inspections, we essentially have no oversight of those manufacturers. A GMP inspection is far more than just a snapshot of that facility the day the inspector arrives. It is a detailed survey of how that plant has been operating for months, which allows a realistic conclusion about whether that facility can and does follow accepted drug production procedures. Relying on testing by the FDA or the U.S. drug company that receives the foreign ingredients is not a substitute for examining the source of production. The GAO notes that FDA today can allocate only about $11 million for its entire foreign drug inspection program. That is far too little an effort for such an important part of our national safety net, but, unfortunately, says a great deal about our current commitment to assuring the safety of those drugs. I urge you to support a level of appropriated funds that will permit FDA to assure that foreign facilities are complying with our standards.

2) **Upgrading FDA's IT systems should be among our highest priorities.** If we don't even have a system for capturing who's making these products, where they are, what's coming into our country, and related critical information needs, we can't hope to begin the process of improving our coverage of imports. The IT systems should be configured in a way that allows the Agency to use a myriad of risk factors, including potential impact on the public health, to direct its inspectional and import efforts. The Science Board recommends increased appropriations of $800 million for FDA's overall IT needs, so there is a long way to go if FDA is to have state-of-the-art information systems, but we could at least start with funding an effective import information system.

3) **Institute a vigorous mechanism for testing drugs for ingredients or contaminants that are not approved for that compound.** History has shown that processors, especially in less developed countries, can be adept at adding substances to increase the value of the product or decrease costs of production. But the danger of doing so, whether it be the industrial plastic melamine in pet food, the polysaccharide inulin in apple juice, or the dietary supplement chondroitin in heparin, is well established, and poses an enormous hole in the safety net we are trying to maintain. Recent events have shown that U.S. processors and the public can be victimized alike by these nefarious activities, and we must find a way to end them.

In conclusion, I believe that the scientists within the Food and Drug Administration have shown that they can effectively assure the safety of drug production when given the tools with which to do so. And U.S. drug manufacturers accept the need for high standards in drug manufacturing and generally adopt those standards faithfully, and many go to great lengths to secure their chain of supply of drug ingredients. Drugs made in the United States under FDA's rigorous quality control standards have an extraordinarily good safety record, as measured by the paucity of manufacturing defects and deaths and illnesses related to manufacturing deficiencies. But it is obvious that foreign sources do not share in that record of success. It does no good to have rules if they are not obeyed, no good to set high standards if they are not used, and no good to develop advanced scientific skills if they are not employed. That countries such as China have a record of serious problems in drug manufacturing is indisputable. And the disparity in drug inspections—in which FDA inspects U.S. facilities regularly and those in China and India almost never—is indefensible. I urge you to make changing that paradigm one of your highest priorities for this year.

Thank you again for inviting me to give my views on this subject.

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Mr. STUPAK. Thank you, Mr. Hubbard.

Mr. Nielsen, please, for your opening statement, sir.

**STATEMENT OF CARL R. NIELSEN, RETIRED DIRECTOR OF THE DIVISION OF IMPORT OPERATIONS, OFFICE OF REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Dr. NIELSEN. Mr. Chairman, members of the subcommittee, I thank you for another opportunity to discuss FDA's foreign drug inspection program, and I hope my participation will help the subcommittee develop effective remedies for a public health and safety system needing serious attention.

The press has been very active the last couple months following the contaminated heparin story. FDA had a press call yesterday and reported there are now 81 deaths associated with the use of contaminated heparin from China. Truly the heparin story is a tragedy that seems to keep growing in magnitude. Because the FDA investigation has not isolated the likely node in the supply chain where the contamination occurred, FDA is encouraging all batches of heparin to be tested. Is that sufficient?

FDA wants to be able to say it would not have made a difference whether the Changzhou plant was inspected earlier, that the contamination would not have been discovered. FDA is responding in its usual react mode to a serious injurious event after the damage is done, not a prevention mode. Granted, the mandatory identity test in each batch of API received by the drug manufacturer would not have identified the contamination, but facility inspections do help leverage safety. I say that the Chinese foreign manufacturer and its suppliers had adhered to good manufacturing practices and control of raw material and if FDA had inspected the plant to verify good manufacturing practices were in place, then perhaps 81 lives could have been saved.

If compliance with the current GMP regulations could not have reasonably prevented or deterred the contamination of the heparin, then it may be time to finally update and rewrite the drug GMP regulations rather than trying to convince industry through nonbinding guidance documents to enhance scrutiny of active ingredients and other components.

The vulnerability of the U.S. Drug supply to imported substandard or counterfeit active pharmaceutical ingredients, or APIs, is not a new issue before the Agency. Beginning in 1991, my colleague Benjamin L. England, who is also appearing on his behalf, another FDA investigator and I initiated numerous international investigations with U.S. Customs related to APIs from several foreign countries, including China.

In my previous testimony before this subcommittee on November 1st, 2007, I stated those counterfeit investigations found evidence that there were deaths associated with the use of carbamezapine, an anti-convulsant made out of imported counterfeit carbamezapine active ingredient. Those investigations also found evidence of imported counterfeit APIs back to the mid-1980s.

Only one of the counterfeit cases was successfully prosecuted. In March 1996, in a plea agreement the defendant admitted the importation of several counterfeit APIs for several years. In May 1996, while I was a senior special agent in FDA's Office of Criminal Investigations, I wrote an internal memorandum to the upper management of the OCI describing the potential threats of harmful im-

purities being introduced into finished drugs by counterfeit APIs and APIs from unapproved sources, and I suggested several strategies to combat the threats of counterfeit APIs.

This memorandum was produced to this subcommittee by FDA during a hearing in June 2000 on the subject of counterfeit drugs. Ultimately, months after I submitted my memorandum, a meeting was held in the Commissioner's office in February 1997 and the imported counterfeit drug problem was verbally declared a top priority. Unfortunately, there was a leadership change at the Agency within a month and the counterfeit API issue largely left the Agency's radar scope.

It seems it takes numerous deaths now to generate a call to evaluate and modify FDA requirements and operations. It has been 8 years since the 2000 hearing on imported counterfeits and 17 years since the first imported counterfeit API investigation. The same regulatory requirements for receiving and accepting components by finished drug manufacturers remain the same:identity tests and certificates of analyses provided by the supplier.

Sadly, when looking at the history of the API problem, it should not be a surprise that it is possible for the recent heparin incident to occur.

It is time for a radical change in improvement and adjustment of agency operations that fits the international trade paradigm and facilitates the trade of safe products. FDA must have a credible presence in foreign markets to better ensure compliance with good manufacturing practices and other requirements that it assure a supply of safe and effective drugs.

The heparin incident demonstrates just how internationally linked we are relative to drug safety. Prescription drugs and over-the-counter medicines may represent less than 10 percent of all FDA imported regulated commodities, but the heparin scenario shows the serious cascading adverse health affects of the contamination of just one common and old drug.

The FDA can be rebuilt, but it will be expensive. The public health cost is higher though if no significant investment is made, as demonstrated by the heparin incident. Effective post-market surveillance activities are essential to FDA's public health and safety mission.

There are many great ideas for steering FDA effectively into the 21st century, but without investment in the integrated IT, execution of the great ideas are not very likely. If the IT development is functionally absent from corrective measures, then we should just plan a 10-year reunion to revisit what should have been known or done to prevent more deaths from contaminated drugs.

The foreign firms may not be in immediate reach for inspection, but the products are. Imported drugs are not going into a black hole.

I thank you for your time and look forward to answering any questions you may have.

[The prepared statement of Mr. Nielsen follows:]

**Statement of**

Carl R. Nielsen

FDA- retired, former Director of ORA's Division of Import Operations and Policy

**Before the**

SUBCOMMITTEE ON OVERSIGHT & INVESTIGATIONS

COMMITTEE ON ENERGY & COMMERCE

U.S. HOUSE OF REPRESENTATIVES

**On the subject of**

FDA's Foreign Drug Inspection Program

April 22, 2008

A. Introduction:

Mr. Chairman, members of the Subcommittee on Oversight and Investigations, I thank you for this opportunity to discuss the status of FDA's oversight of the foreign-based pharmaceutical manufacturing industry and related drug products. I retired from FDA in February 2005 after 32 years of government service, 28 of which I served in the U.S. Food and Drug Administration, Office of Regulatory Affairs (ORA). Besides serving as a senior special agent with FDA's ORA/Office of Criminal Investigations, I served in capacities as a consumer safety officer carrying out duties as a field investigator, a resident-in-charge, a field compliance officer, a first line supervisor of a field unit dedicated to import operations, lead compliance officer with the original Team Biologics Core Team based in ORA headquarters, and, finally, for nearly six years, I served as Director of ORA's Division of Import Operations and Policy (DIOP). Since

my retirement I have been self-employed as a regulatory consultant and am founder and owner of C. Nielsen Consulting, an FDA regulatory consulting business.

B. Foreign Inspections and Drug Safety:

The inspection or audit of foreign manufacturers of components (including active pharmaceutical ingredients) and finished drugs is a critical activity to ensure the drug industry has implemented appropriate manufacturing steps and controls to ensure each batch of drug meets all product specifications and is safe. Basically, the facility inspection process verifies the facilities and equipment are adequate in design and construction, and verifies the manufacturing processes, and the quality control and testing procedures are in place and executed for each batch of drug product. FDA uses the designation "state of control" to characterize a firm that has implemented and adhered to good manufacturing practices that best ensures drug safety and effectiveness. The best manufacturing practices may include the testing of in-process materials, testing of air handling systems, testing of equipment performance, testing of cleaning operations between batches of production, testing of water systems, and the testing and monitoring of a myriad of other potential variables that, if left uncontrolled, could result in contaminated finished drug product or otherwise render the finished drug product unsafe or ineffective. There is not a battery of finished product testing that can replace good manufacturing practices to ensure the product safety and effectiveness for each dose of drug. If one just relied on finished product testing for product safety and effectiveness without regard to a controlled manufacturing process, then each tablet, pill, capsule, or vial would have to be tested to provide a 100% assurance the products are safe and

effective. Obviously, it would not make sense to destroy the entire production just for testing purposes.

The credible presence of an FDA inspection process can help provide some additional incentive for foreign industry to implement all the best practices to ensure the delivery of a safe and effective drug supply in the global marketplace. Certainly a foreign firm that knows there is a strong likelihood of being subjected to routine FDA inspections or equivalent will have greater incentive to have the manufacturing house in order for FDA product safety requirements. However, the current level and frequency of FDA foreign inspections is woefully wanting, regardless if the number of foreign prescription drug manufacturers to be inspected is 3,000 or 6,800 or many more.

The effectiveness of inspections is not just a matter of how frequently a firm is inspected, but also the quality and depth of inspection which is dictated, in part, by the inspector's expertise, available funds, and the time allowed by management for conducting the inspection. Foreign inspections are generally much shorter in duration compared to inspections of drug firms in the United States. The February, 2008 FDA inspection of Changzou SPL Company, Ltd., Changzou City, Jiangsu Province, China, conducted as a follow-up to the recent Heparin problems was five (5) days in duration according to the FDA-483, Inspectional Observations, posted on FDA's web site. It would be reasonable to expect an inspection of greater depth of at least twice as long or 10 days would have occurred if the subject plant and supply chains had been located in the United States rather than China.

C. FDA's Foreign and Domestic Inspection Program + Funding:

The FDA's Office of Regulatory Affairs (ORA) conducts the foreign inspections. There may be inspection team members from other FDA components, but generally ORA has the responsibility for accomplishing "X" number of foreign drug inspections per year as identified in the ORA Workplan. Inspection guidance is provided to the inspectors through a variety of documents. As an example, guidance for conducting domestic/foreign drug manufacturing inspections is primarily given through the Compliance Program Guidance Manual (CPGM) # 7356.002, entitled "Drug Manufacturing Inspections". Many of the programs are posted on the FDA web site under the "Manuals" link, including the cited program. The CPGM's articulate the rationale and strategies to be used by the inspectors for evaluating a firm's compliance with FDA requirements.

ORA is not directly funded for inspections and other post-market activities and must negotiate with the Center for Drug Evaluation & Research (CDER) through a work plan process to determine how many foreign inspections can be funded for the year. Generally, resources are allocated in the form of a Full-time Equivalent (FTE) by program for the year. The ORA work plan identifies the number of FTE's allocated to specific programs and related activities. The FTE is largely a time management tool. Less than 1 FTE may be allocated for a particular activity for a particular product category. Reportable activities for which inspectors and laboratory analysts report time spent

include facility inspections, sample collections, sample analyses, investigations, product examinations and entry review for imported drugs.

FDA's budget process and method of allocating resources is very confusing. In my previous testimony before this Subcommittee on November 1, 2007, I referred to a statement by former FDA Deputy Commissioner for Policy William B. Schultz before the Permanent Subcommittee on Investigations of the Senate's Committee on Government Affairs on September 24, 1998. Mr. Schultz provided information relative to the meaning of a "supported FTE". He said 565 FTE's translates to 314 "operational" staff or 112 actual investigators and 202 bench analysts. Apparently 251 of the 565 FTE or 44% of the FTE is required to support 314 personnel who conduct inspections and analyze samples and actually report time into the accountability system for program management.

As this Subcommittee reviews budget needs and considers legislative remedies to improve FDA oversight of regulated industries, I strongly suggest the current FDA budget process, the FTE model and ORA work plan process be evaluated and modified as needed. If significant new resources are provided to the Agency and the current system for work planning and allocating resources is used for deploying or allocating the resources, a newly funded 565 FTE, could result only in 112 inspectors based on historical management practices. This scenario in part explains why I was never able to obtain a roster of field inspectors/investigators dedicated to import operations during my nearly 6 years as Director of ORA's Division of Import Operations and Policy. The

current program management practice emphasizes FTE that may not be directly related to the location of trained individuals available to perform specific tasks in a particular geographic area.

D. Post-market Activities & Information Technology:

FDA's Office of Regulatory Affairs (ORA) is the organization that manages and supports all field operations. Primary post-market activities conducted by ORA include domestic/foreign inspections of all regulated commodities and industries; laboratory analyses; receiving and following-up consumer/trade complaints; monitoring product recalls; conducting investigations, and conducting import operations at the ports of entry.

The FDA Science Board's Subcommittee on Science and Technology Report, "Science and Mission at Risk" identified many weaknesses with the existing FDA infrastructure without evaluating in detail the current status of ORA's Information Technology (IT) needs. Just as the Science Board identified the need for enhanced post-market data to better enable product Center oversight of product safety, ORA also needs post-market information in an integrated fashion for use in a risk management approach. Daily priorities for a variety of activities must be established quickly regardless of the ORA staff size and location. The Science Board or a similar third party source should thoroughly assess ORA's infrastructure and processes in order to develop a meaningful proposed budget that could translate into remarkable improvement of public health and safety. ORA represents a primary front-line force that interacts directly with the

consumers, industry, and other federal and state government agencies in the post-market environment.

A risk based approach by FDA for determining admissibility of imported goods and preventing entry without verification of compliance can not be effectuated without significant investment in an integrated IT capability. ORA must use information from each of the Agency product Centers, including CDER, in order to make risk based decisions at the border and to plan inspections and other activities in a manner to best mitigate the greatest potential risks to public health. The development of a comprehensive risk model for a specific product includes both pre-approval and post-market information, i.e., inherent risks + product experience. Information related to product stability, recalls, adverse event reports, consumer/trade complaints, compliance with good manufacturing practice regulations, epidemiological information, exogenous information, and other relevant factors can contribute to a workable risk-based regulatory approach to drug safety and effectiveness in the global market. But effectiveness of a robust risk based approach is contingent on the development of appropriate IT for executing the regulatory approach. FDA must stop relying on its paper driven systems and move away from the "call X person who knows" or "find the memo" model of information sharing.

E. Solutions are not just more of the same:

Although significant new resources are required, those resources should not just be thrown to the Agency with a hope of better things to come based on the size or amount of new resources. Radical changes are needed in the organizational structure, management and IT systems to significantly improve Agency operations. All relevant product and facility based information, including drug applications, held by the Agency needs to be stored electronically in a readily searchable form for specific purposes. Many old drug applications and drug master files are still in paper form, which means the information is not readily available for use by the ORA field force to determine admissibility of imported drug products. It is not uncommon that industry has to spend significant resources providing hard copies of supplements to drug applications to local field offices as evidence of compliance of shipments of drugs offered for import even though the regulated firms have followed the regulatory requirements and properly submitted supplements and received approval letters from CDER. Not only does the current state of the broken, outdated FDA IT infrastructure pose increased risks to FDA functions and public health, it also increases the cost of doing business for both FDA and industry.

An effective FDA of the future must have the IT capabilities to support an "account" based approach for all regulated and registered facilities. The "account" should be a single, verifiable, unique, firm identifier as an anchor to which all historical and relevant information held by FDA is linked. There should be an FDA IT capability to enter a firm name, address and/or registration number to obtain a profile based on an automated rapid search of related information such as the drug applications, drug master files, drug labeling, FDA inspection reports, FDA laboratory results, recall histories, adverse event

reports, compliance histories, and importations into the United States. The same or similar information could then readily be applied to risk-based decisions by the Center and ORA during the course of targeting scant resources towards products that pose the greatest potential threat to public health.

The drug facility registration and product listing information submitted to and stored by FDA needs to be verified at the time of submission, and there needs to be a grandfather verification process for drug firms already registered and listed. The establishment of such a gatekeeper role would improve data integrity so a reliable data set could be used in administrative processes related to the registration and product listing. Legislation should be considered to make the firm registration process similar to an FDA "license" or "permit" for importation. Congress should consider promulgating FDA authorities to grant, deny, suspend, revoke, and re-instate registration based on the compliance status with FDA requirements. Linking an affirmative compliance status with registration information could transform the current registration process into a meaningful risk based system. Additionally, the establishment of a single unique account identifier for registered firms could enhance the effectiveness of FDA's Import Alert system. Firm identifiers and FDA product codes are critical elements for effective selectivity criteria when targeting shipments for interdiction or for expediting entry.

FDA's ORA organizational structure has remained basically the same over the last three decades with most resources devoted to oversight of regulated industry within the United States. Volunteers are solicited from the domestic inspection force to conduct foreign

inspections with varying success. Resources allocated for foreign inspections and oversight of imported products is nominal compared to resources for overseeing the domestic drug industry. The FDA ORA infrastructure and management systems are largely controlled by career government officials with interest towards preserving traditional domestic based operations. The lack of direct funding for ORA further aggravates the current dysfunction in the arenas of foreign inspections, border operations and IT development. Therefore, the Agency should be encouraged, if not mandated, to establish an organization funded and empowered to specifically oversee foreign regulated industry, traditional border operations, and the FDA import community. Such an organization would be better positioned to evaluate and monitor the entire supply chains or product life cycle of foreign made products to better ensure the delivery of safe products to the U.S. markets.

The findings from a robust foreign inspection program supported by effective IT would provide relevant information for targeting higher risk goods for examination at the border or for expediting movement of compliant goods. Inspections of product and receiving processes at the importer level could also generate relevant information for risk based targeting at the borders, and provide relevant information in selecting foreign firms for inspection. The establishment of a directly funded FDA designated unit for covering foreign industry, border operations, and importers with line authority to inspectors on the ground in the United States and foreign posts would best ensure efficient and effective use of government resources.

Mr. STUPAK. Thank you and thank you for your testimony. Mr. England, please, your opening statement, sir.

**STATEMENT OF BENJAMIN L. ENGLAND, ESQ., BENJAMIN L. ENGLAND & ASSOCIATES, LLC, AND FDAIMPORTS.COM, INC.**

Mr. ENGLAND. Thank you, Mr. Chairman and members of the Committee. I am Benjamin L. England, founder and owner of an FDA consulting practice called FDAImports.com, practicing attorney, and I represent foreign and domestic food, drug, medical device, and cosmetic companies in matters that involve the FDA.

I am a 17-year veteran of the FDA. My written testimony, which is supplied for the record, discusses my background in greater detail. I am not going to belabor it here. I am pleased that the subcommittee has taken up the initiative to press for solutions for managing these safety risks associated with imported products again and to focus today specifically upon FDA's foreign drug inspection program.

I am troubled that we are again meeting in the shadow of adverse events that have claimed the lives of American consumers, and we are still hearing about what FDA is doing after the fact.

The last time I appeared before you I had made mention of the counterfeit bulk drug investigations of the 90s as well. And I might—Mr. Nielsen just recounted his efforts to improve the FDA's investigation of imported counterfeit drugs which was most likely, at least in my opinion, quashed at some point in the Agency. In fact, when Mr. Nielsen left OCI—I am going to tell a story on him and he doesn't know I am going to do it—but when he left OCI and eventually reported to his job as the Director of the Division of Import Operations and Policy, he indicated to his supervisor, his new supervisor, that he was looking forward to getting back to finding ways to prevent counterfeit drugs from other countries into this country, to which his supervisor asked, what counterfeit drugs?

This heparin incident apparently occurred because of some human error in deciding inspection had already been conducted or should be conducted. I believe that we are on the brink of a series of these events and that waiting for FDA's timeline will be a mistake. The time for developing strict strategies is long past.

As I said months ago in the press and to your staff, Mr. Chairman, this recent case appears to be the close cousin of the counterfeit drug cases discovered nearly 2 years ago—2 decades ago, excuse me.

At that time, the illegal conduct was discovered through intensive smart facility inspections and by the efforts of forward thinking forensic scientists and investigators. This occurred only because of the intellectual connection between certain domestic inspections at U.S. facilities by a keen FDA investigator who had previously conducted the foreign inspection of the bulk supplier, coupled with follow-up inspections at the foreign supplier, which were themselves targeted with knowledge of where evidence of illegal conduct was likely to be found. It is no different today except that we now have available to us significantly improved technological solutions that may prove more useful to more precisely and efficiently identify, target, and intercept safety risks prior to the realization in the marketplace.

I will provide now just a summary of six of my recommendations, and at this stage I believe that they are basically in the order of priority I would put them at. One, it is axiomatic that FDA's data systems, operational and management systems alike, have become the breeding grounds for potential disasters. Now let me be clear. That is not to say that all the products being imported or distributed into the U.S. are dangerous or even high risk. Rather, the relative risk of any of them is not known by the FDA. The agency can barely manage to do more on a daily basis than to check for registration numbers, listing numbers, and on a very good day some Establishment Evaluation data. When determining whether imported drugs should enter the country, the systems remain badly stovepiped or siloed and FDA's proposals will take at least another 5 years to correct them. FDA's solutions appear primarily to be to lay a common portal over the systems, which will not actually integrate the legacy systems.

Number two, FDA does not conduct enough foreign GMP surveillance inspections to constitute a regulatory force in the world, even though the prized markets for such articles is here in the United States. The agency should be required to conduct foreign good measuring practice inspections at the same frequency as domestic inspections. Even without additional funding this would level the relevant risks between domestic and foreign sources of drugs and would force the Agency to balance those risks against the two sources.

The cGMP surveillance inspection, when conducted by competent investigators who have at their disposal integrated account-based information covering the life cycle of products manufactured by the facility, remains the single most effective means for detecting the kinds of activities that have been prevalent in the counterfeiting of drugs, the production of articles using unapproved sources of materials, and product substitution. Without a rigorous foreign inspection program FDA will never prevent the next product contamination before it causes illness or death.

Three, throwing more money at FDA without requiring the resources to be used to produce different outcomes will produce diminishing returns. In my opinion, I believe the most critical area for increasing funding is in FDA's IT systems. FDA systems must be far smarter and must be capable of taking data from a variety of sources, both internal and external, for comparison against legacy data. Its operational systems must utilize risk-based algorithms, designed to predict where an exertion of agency effort will yield positive and measurable safety and security results.

Without a major reinvention of FDA's IT systems, even the hundreds of proposals that were in the 2003 import strategic plan are of limited value. And following that, I would dramatically increase the resources in the field inspection force to include dedicated foreign inspection cadres, funding to increase laboratory capacity, funding for leveraging State inspections for FDA's domestic operations, and enhancement of those few headquarters components that are capable of actually assisting the field operations.

Four, in order to take the most advantage of enhanced IT systems, the Agency should begin moving immediately to an account-based regulatory approach that enables the interconnectivity of

regulatory processes along the entire life cycle of its products to encompass all steps from application and approval, where required, to the consumer impact.

FDA could learn a lot by understanding how Customs has moved from a transaction-only approach to an accounts-based approach that evaluates the transaction in the context of the account.

Customs has accomplished much of this by requiring each submission of the data to be connected to a unique numerical identifier. These identifiers can be related to one another enabling cross-linking of companies that demonstrate interrelationships.

Under the current regime the lack of integration of data accounts means a human must notice slight differences in company names to assess whether a foreign drug facility has been ever inspected, and in this regard a unified registration system could quite easily have prevented some of the deaths as well.

Five, I believe the organization of the Agency contributes to its inefficiencies. I recommend again establishing within FDA an organization that reports to the Commissioner with the mission of focusing on enhancing the safety of foreign made products, all products.

I continue to believe fixing FDA's import and foreign inspection problem requires it to be broken free from the domestic operation, which produces much of the bureaucratic inertia against change in this area.

This new organization would be responsible for all important international-focused work-planning activities, conducting facility inspections of foreign processors and importers, overseeing and conducting border operations, conducting foreign government and industry assessments and training, and support trade negotiations in a manner to enhance safety of imported products.

And to accomplish this, the new organization should be directly funded rather than receiving its funding through the product centers. A basic persistent infrastructure to manage risk associated with all imported commodities must be maintained regardless of the year-to-year changes that may appropriately occur in program directions.

And six, and finally, perhaps an unpopular solution to some involves the use of some third parties. In my opinion, FDA should begin obtaining as much information as it can from as many reliable sources as the Agency can find regarding the cGMP compliance status and supply change security programs of foreign drug facilities that are not inspected by FDA and are not ever going to be inspected by the FDA.

Additional risk data could come in the form of third party inspection and certification companies, accompanied by a robust auditing process on both sides of the border. All such data should be connected to the firm's unique identifier and incorporated into the account data to permit its assessment in light of other legacy and other agency data. This recommendation would permit the Agency to focus its import inspection and examination efforts on shipments representing known and unknown risks.

And I thank the subcommittee Chair and the members for the opportunity to discuss these important issues again.

[The prepared statement of Mr. England follows:]

## STATEMENT OF BENJAMIN L. ENGLAND, J.D.

### 1. INTRODUCTION

Mr. Chairman and Members of the Committee, I am Benjamin L. England, founder and owner of an FDA consulting practice, FDAImports.com, Inc., and a practicing attorney representing foreign and domestic food, drug, medical device and cosmetic companies in matters involving the U.S. Food and Drug Administration (FDA). I am a 17-year veteran of the U.S. Food and Drug Administration (FDA). From 1986 to 2003 I held the positions of Regulatory Microbiologist in FDA's Baltimore Microbiology Laboratory, Consumer Safety Officer and Compliance Officer in FDA's Baltimore District Office, Special Agent with FDA's Office of Criminal Investigations in the Miami Field Office, Compliance Officer in FDA's Miami Resident Post, and Regulatory Counsel to FDA's Associate Commissioner for Regulatory Affairs (or ACRA) in Headquarters. I resigned my most recent FDA position as Regulatory Counsel to the ACRA in July 2003—a position I held in FDA for over 3 years as a Title 42 appointee. During my last 3 years at FDA, I was a key point person for Customs and Border Protection, I chaired the FDA's Counterfeit Drug Working Group, instituted the Joint Agency-Industry Working Group to combat product counterfeiting and tampering, which laid the ground work for the preparation of FDA's initial Counterfeit Drug Task Force report, and co-chaired FDA's Import Strategic Plan Steering Committee.

Along with my colleague, Mr. Carl Nielsen, who is also before you today testifying on his own behalf, I established the Agency's first series of Import Enforcement Training Courses, and with a few dedicated FDA and Customs officials, trained nearly every FDA import inspector, investigator, import program manager, and compliance officer in the effective use of Customs enforcement tools against products imported in the U.S. in violation of FDA requirements.

At the outset, I am pleased the Committee has taken the initiative to press for solutions for managing safety risks associated with imported products—and to focus today specifically upon FDA's foreign drug inspection program. I do not feel it is necessary to reiterate all of the history in this testimony, as it is a part of the record from previous hearings. Some points, however, bear repeating. Further, since my last appearance before you on November 1, 2007, more evidence has appeared in the U.S. marketplace laying bare the brokenness of the regulatory and information technology (IT) systems FDA is hobbling along with and the real safety risks that attend the Agency's present condition.

I highlighted in my previous testimony the counterfeit bulk drug investigations of the 1990s, which were all but abandoned by FDA. We discussed how reminiscent those cases were to press accounts identified by the Chair related to counterfeit articles, both finished and bulk, in any number for foreign markets. Today we are confronted with serious adverse events involving a widely used drug product that appears to have been made using substituted active ingredients at a foreign facility that was never inspected by FDA—because of some human error in deciding whether an inspection had already been conducted or should be conducted. I believe that we are truly on the brink of a series of these events and that waiting for FDA to take some action that actually mitigates risk or encouraging the Agency to act unilaterally will be an exercise in futility. As I said in the press and to your staff, Mr. Chairman, this recent case appears to be the close cousin of the same conduct discovered nearly two decades ago. At that time, it was through intensive and smart facility inspections and by the efforts of forward thinking forensic scientists and investigators the activity was discovered. Moreover, the successfully prosecuted counterfeit bulk drug case was made possible only through the intellectual connections between certain domestic inspections at U.S. facilities by a keen FDA investigator who had previously conducted the foreign inspection of the bulk supplier, coupled with follow up inspections at the foreign supplier, which were themselves targeted with knowledge of where evidence of illegal conduct was likely to be found.

It is no different today—except that we now have available to us significantly improved technological solutions that may prove useful to more precisely and efficiently identify, target, and intercept safety risks prior to their realization in the market place.

### 2. INTEGRATING THE SOLUTIONS ACROSS THE AGENCY

One of my greatest concerns as a former FDA official and a current consumer is that Congress would jump to solutions that are as "stove-piped" or "siloed" as the Agency. This is particularly true with regard to FDA's information technology systems. As the General Accountability Office (GAO) has articulated several times over

the last 15 years, the Agency's legacy data systems are antiquated and not integrated. The FDA has been striving for decades under a budget that is anemic with regard to IT funding. Most Americans, I presume, would find it quite astonishing that FDA personnel (humans) must make decisions about whether a foreign facility should be (or has previously been) inspected by reading the name and comparing it to names in a number of data systems.

Even more astonishing would be the realization that FDA's various registration systems—across all of its Centers and regulated commodities—are not relationally integrated to background agency data or to its operational systems. Humans are still entering data bases and checking to see if a registration, supplied during the importation process is "in" the system and whether the number "belongs to" the manufacturer declared in an entry. FDA still receives its manufacturer declarations via the Customs Manufacturer Identification (MID) process and that MID must be translated in FDA's systems to its own numbering system. Because of the variations in the MID process, FDA ends up with duplicate or triplicate numbers for the same facility—or far worse. Portal overlays can help reduce the number of data base user names and passwords an FDA official may have to remember—but they will not integrate data. These realizations, among others, account for at least some of the discrepancies in the Agency's data with respect to how many foreign facilities have been or should be inspected. This is an annoying result. But it is more than annoying when the lack of integration of data accounts for a regulatory regime which relies on a human to notice slight differences in company names to assess whether a facility has ever been inspected. In this regard, a unified registration system could quite easily have prevented the recent heparin scenario.

## 3. MORE THAN COUNTING COMPANIES

Although it is critical for FDA to be able to define its universe, regulatory oversight requires far more than counting. It is critical that FDA is able to obtain reliable and affirmative evidence that foreign facilities manufacturing drugs for the U.S market are operating within the scope of FDA's current good manufacturing practices (cGMP) requirements. This information can be derived from a number of sources—but one primary and historical information source has been the physical FDA inspection of the facility making the bulk active pharmaceuticals and the finished dosage drugs. As discussed in previous testimony, the drug manufacturing industry has undergone significant changes over the last 15 years in how and where its bulk actives and finished drugs are prepared, packed, and labeled. Many more drugs are manufactured in foreign jurisdictions now than ever before. FDA's inability to count those facilities is indeed troubling. But the point of being able to count them must be based upon FDA's ability to conduct adequate oversight of how they manufacture the drugs we take. I might add that without a number we can all point to, you are also unable to assess how FDA is doing in evaluating the safety and effectiveness of those drugs. Confidence in the system understandably erodes.

The post-marketing surveillance inspections of drug and medical device facilities are absolutely critical to assessing the quality, purity, safety and effectiveness of the articles they manufacture. I have never heard FDA or the domestic industry as a whole say otherwise, although I am sure there are different opinions as to the absolute frequency that should be applied. Further, the sophistication of the inspector, the sufficiency of agency inspection guidance, the amount of time the facility is available to the inspector, and the depth and scope of the inspection all play significant roles in the reliability of the inspection results. The frequency of cGMP surveillance inspections correlates directly to the level of confidence FDA and the consumers enjoy respecting the critical elements of the articles.

The cGMP (or Quality System) requirements are intended to address the adequacy and appropriateness of the manufacturing process, the design of that process, the equipment used in the process, the control and adequacy of raw materials subjected to processing, the source of those ingredients, the qualifications of the facility's critical personnel, the packaging, labeling, and failure evaluation processes, and post-distribution monitoring, including company recall procedures. FDA's current inspection frequency for foreign prescription finished drug and active ingredient manufacturers is reportedly on a 13-year inspection cycle. FDA is required to inspect corresponding domestic drug facilities on a 2-year cycle. When you compare this foreign facility inspection cycle (for Rx Active Pharmaceutical Ingredient manufacturers alone) to the increase in the numbers of imported drug shipments over the last 10 years, one can see its impact historically and can predict that impact prospectively.

For instance, according to FDA data, from 1991 to 2000 the number of FDA-regulated import shipments increased by 272% and in 2001 alone there were more than

7 million imported commercial lines of entry.[1] In 2002, approximately 7.8 million lines of FDA-regulated commercial shipments were imported. From 1997 to 2002, the number of imports of every kind of FDA-regulated product at least doubled. In 2007, FDA had jurisdiction over more than 17 million imported commercial lines of entry under its jurisdiction will be imported. This represents two doublings in the sheer number of entry transactions every five years since 1997. FDA's inspection resources directed at assessing the safety of imported products and evaluating the manufacturing systems of foreign facilities has remained static throughout that time period.[2]

Based upon my experience at FDA, which is further informed by statements from FDA in the press and in testimony before various congressional committees, roughly 60% of the total number of commercial lines of entry consists of food imports; 25% consists of imported medical devices; and 10% consists of imported drugs and biologics. Using these proportions, FDA is responsible for ensuring the quality, safety and efficacy of nearly 2 million imported drug shipments per year.

As I testified in November 1, 2007, FDA's list of "uninspected" foreign API manufacturers exporting to the U.S. ranged from 242 to 4,600, depending upon the criteria used to populate the list.[3] The reasons for such disparity include the FDA's multiple, "siloed", antiquated and non-integrated IT systems; the lack of a meaningful gatekeeper for the Agency's drug establishment registration process; and the Agency's insistence to mitigate the usefulness of FDA's historical import entry (OASIS[4]) transactional data.

Today, it is apparent that all of these factors persist at FDA and the Agency is still struggling to identify the scope of the universe of foreign drug firms under its jurisdiction—whether we speak in terms of all foreign firms exporting drugs for human or animal consumption or merely foreign firms that FDA believes "should be" inspected. Lacking the ability to identify the larger, total universe of foreign drug firms exporting drugs to the U.S., the attempt to reduce that total to a more manageable "high risk" universe for targeting inspections has little foundation in reality. Consequently, FDA's current range of foreign drug firms exporting drugs to the U.S. that should be inspected by FDA is from 3,000 to 6,700.[5]

So at present, FDA is tasked with evaluating the safety and effectiveness of nearly 2 million imported shipments of drugs from as many as 6,700 foreign facilities, any number of which have not been visited by an FDA inspector for as long as a decade (or have not been visited at all, as in the case of the Chinese supplier of heparin potentially linked to 81 deaths in the U.S.). FDA is doing this with an IT system that contains multiple duplicate or triplicate facilities with different or non-unified numerical identification systems, literally dozens of data bases that are dis-

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[1] A commercial line of entry is the equivalent of a line on a commercial invoice covering the sale of a product from a foreign exporter to a U.S. importer, owner, or consignee. A line may consist of a single laser DVD reader from Taiwan, regulated by FDA as an electronic product, or it may consist of 10 x 40 foot refrigerated containers of cantaloupes from Mexico. With regard to drugs, a line may be a shipment of 10 cases of retail ready over-the-counter (OTC) tablets of acetaminophen or a container of several metric tons of relatively pure bulk active pharmaceutical ingredients. A single invoice may have one or dozens of lines. FDA counts its import transactions by commercial line of entry. Each FDA-regulated line is subject to FDA jurisdiction based upon the legal definitions of the various products in the FDCA.

[2] More regretfully, even though roughly half of all FDA-regulated products consumed in the U.S. are either manufactured in whole or in part in a foreign country, as I recall by the summer of 2003 approximately only 7 out of every 100 dollars spent by FDA regulating products under the Agency's jurisdiction was focused on FDA's import or foreign programs.

[3] See Statement of Jane E. Henney, M.D., FDA Commissioner, Before the Subcomm. on Oversight & Investigations, Comm. on Commerce, U.S. House of Representatives, http://www.fda.gov/ola/2000/counterfeitdrugs.html (Oct. 3, 2000).

[4] "OASIS" is an acronym that stands for FDA's "Operational and Administrative System for Import Support." See FDA's discussion of OASIS at http://www.fda.gov/ora/import/oasis/home—page.html.

[5] These numbers are derived from two separate FDA data systems and thus the disparity. The lower number is reportedly from FDA's Drug Registration and Listing System (DRLS). The higher number is a downward departure from data stored in ORADDS, the OASIS data warehouse. Therefore, the lower number is taken from the process whereby foreign manufacturers report data to FDA in order to meet two of the most basic minimum requirements to export drugs to the U.S.: drug registration and drug listing; and the higher number is taken from the process whereby Customs brokers report to Customs and to FDA through OASIS the identity of foreign manufacturers actually exporting drugs to the U.S. This discrepancy alone is troubling. It is unclear over what time frame the two numbers were derived and whether they correlate. Further, it undercuts FDA's traditional argument that OASIS data is unreliable simply because it represents self reporting through the importation process. DRLS also represents self reporting to FDA, and in the import declaration environment, there is another agency, Customs and Border Protection, that strictly governs and enforces proper data reporting.

connected, and a couple hundred people on a part time basis. This certainly seems to be a resource problem—but it is far more than that.

### 4. WHY NOT JUST SAMPLE MORE?

As stated in my previous testimony, when FDA is virtually absent in the foreign market assessing compliance with cGMPs, the Agency is left with attempting to assess risks associated with foreign sourced drugs and drug ingredients using its import operations. The FDA's current import program, however, focuses primarily on FDA approved application, facility registration, and drug listing database submissions, label reviews, and finished product testing. These approaches are incapable of assessing the cGMP compliance and therefore the quality and safety of imported drugs. Although testing can tell FDA something about the quality and even the safety of an imported product, finished product testing at the border (or anywhere along the supply chain) is not a statistically valid method for predicting the safety of later or earlier untested shipments—even other shipments from the same processor.

Where product (and patient) safety is so dependent upon an ongoing and rigorous manufacturing quality system, finished product testing is not even a valid way to determine product safety within the same shipment. Compliance with FDA's drug cGMP program is the only (current) framework within which the Agency can justify relying upon the results obtained from finished product test. Finished product testing is confirmatory only. Without an assessment and understanding about the conditions of manufacture within the facility, the finished product test results are anecdotal at best. Such an approach cannot predict, measure, assess, or assure drug safety.

Any question about this premise is laid to rest with a simple observation from a recent drug safety crisis. FDA now is maintaining that because it took some time for any number of laboratories to identify the contaminant in the heparin, which has caused such tragic loss of life recently, the FDA concludes that there are "limitations as to what inspections can tell you." This is an appalling and irresponsible position. To the contrary, the absence of a meaningful and recurrent FDA inspection presence has far more to do with the events of recent months than almost any other factor. The evidence as to product safety (and security) is found only in the facilities and companies that make and move products into the U.S. market. Lacking a robust foreign drug inspection program, which takes into consideration all elements of prescription and non-prescription foreign drug manufacturing in its scheduling and preparation, promotes a "catch me if you can" foreign drug compliance culture.

I would only add that if FDA's IT systems were capable of linkage using a unique numerical identification system with some level of verification of registration data, then I dare say the system could be designed to flag any submission to the Agency, linked with the unique numerical identifier, with an on screen warning that the facility submitting the data has not be inspected by the Agency. This alone would have enabled FDA to assess whether the manufacturer of the heparin should be approved as a source for the finished dosage manufacturer. Instead, FDA personnel had to resort to recognizing slight variations in the names of two firms.

### 5. ACCOUNT-BASED OVERSIGHT PROVIDES ADDITIONAL BENEFITS

Other government agencies having regulatory oversight over hundreds of thousands of companies, transactions, and compliance procedures have begun to move to account-based regulatory processes to integrate the many steps the agencies must take to assess risks. For instance, Customs, with more than three times the number of import transactions, the responsibility for enforcing virtually every federal law in the importation arena, and the added weight of ensuring the security of imported products and our port infrastructure, has moved to account-based processing. As FDA notes in its various import safety proposals and (purported) risk-based food safety plans, Customs' development of its Automated Commercial Environment (ACE) and the International Trade Data Systems (ITDS) will assist the government in improving its interoperability. However, FDA's background data systems (managing, for instance approval submissions, registrations, listings, 510(k)s, Food Canning Establishment registrations, bioterrorism registrations, drug master file submissions, to name a few) will not be integrated with the final implementation of ACE or ITDS. Although Customs will require a unique numerical identifier from any company providing data into its systems (and for any company identified in such submitted data), FDA will still have to translate that unique identifier into its own registration system—and back into its duplicative, disconnected systems. So it is true that FDA will be able to obtain its import data from one place—as will the

other border agencies—however, FDA's own systems will remain disconnected, non-integrated and stove-piped.

If FDA moved to an account-based system to regulate products in the supply chain, wherever they may be found, and if FDA only accepted data when a Customs-comparable unique numerical identifier is provided with the submission, the Agency would be able to begin the process of internal data integration and meaningful data connectivity with Customs and other border agencies. Inspectional data, import data, adverse event data, and submission data could all be connected via the unique numerical identifier. The data systems could then be connected to FDA's operational data systems (FACTS and OASIS) to permit integration with importation data transmitted by Customs and to help target domestic and foreign facility inspections and border evaluations, inspections, and sampling. The account-based system would develop over time eliminating the now ever-present duplications in firm data and would enable FDA to actually identify the scope and size of the "hay stack" as it exists in the real world. [6]

With an account based regulatory system, the assessment of user fees (or review fees) can be predicted with greater specificity, FDA can identify the size and scope of its regulated industry, modifications, mergers, and facility closings can be identified and tracked, post-market events can be connected to product source, objectionable conditions observed at manufacturing facilities can be tracked through supply chains more readily, supply chains are more transparent and interagency coordination improves dramatically. These are just a few of the benefits.

## 6. CONCLUSION

### A. Missed Opportunities for Change

In conclusion, I reiterate my previous testimony regarding steps going forward. The efforts of over 100 dedicated FDA personnel from all of FDA's product Centers, the Office of Regulatory Affairs (ORA), the field offices, the laboratories, the various information technology offices, and the office of international programs should be presented to Congress and industry in an open forum to enable the Agency to learn risk in the real world. FDA's foreign drug inspection program is only one means for FDA to assess and mitigate risks related to imported drugs. Foreign sourced drugs, whether finished or ingredients, active or inactive, must also pass through the bottleneck of FDA's and Customs' import assessment. Although it is true that FDA's import program is woefully inadequate today, only addressing imported drug risks in terms of increased foreign inspections leaves open risks that may arise in between foreign inspections (even if conducted every 2–3 years) or in the product supply chain (e.g., product counterfeiting, commingling, or tampering). Further, as FDA will never cross enough foreign thresholds to enable the Agency to apply inspection data on all imported drug shipments—more than just additional resources for foreign inspections is needed.

Shortly after September 11, 2001, FDA's Leadership Council established an Import Strategic Plan Steering Committee. By spring 2003 the Import Strategic Plan was virtually complete. FDA developed the ISP from the contributions of more than one hundred Agency experts in all product Centers, field and headquarters components, laboratories, international programs staff, the General Counsel's Office and the Office of Policy, Planning and Legislation.

The ISP's principles were simple but far reaching: Push the current FDA import evaluation process from the extremely limited border transaction to a life-cycle process, which:

- Intentionally gleans information from all points along an article's supply chain;
- Assesses that information based upon FDA requirements and risk of harm;
- Delivers the assessment to border inspectors, compliance officers, and electronic screening systems for reliable targeting decisions; and
- Results in the facilitation of safe products and enforcement against products that are unsafe.

The significance of the ISP and its proposed action items rests in what it represents: an internal agency demand for a dramatic shift in thinking about the identification, assessment and mitigation of risks in the international supply chain.

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[6] In my view, the unique numerical identifier should be site specific and should be capable of verification by government and private systems and processes. Because of the amount of consolidation that can occur in any economic market, whether developed or developing, the identifier must be able account for mergers, acquisitions, business closings etc. Consider, for instance, the ownership changes that can occur over the current FDA foreign inspection cycle of 13 years. Entire countries can disappear or newly emerge in the same geographical location over that amount of time.

Many of the ISP proposals are indeed costly. However, many could have been implemented nearly immediately and would have begun the process of increasing FDA's import efficiency and effectiveness using existing resources. It is this shift in thinking that FDA's middle and upper management seems to continue to resist. I believe that all involved in the ISP process recognized the import problems—even in 2003-are complex and cannot be solved with FDA's traditional regulatory approaches and philosophy.

### B. Some Proposed Changes Going Forward

First, any action by this Subcommittee should include a significant resource investment targeted directly for reengineering FDA's stove-piped IT systems. IT improvements recommended in the ISP are a contingency for executing any serious risk-targeting strategies for foreign inspections and import interdiction of unsafe drugs. This investment, however, cannot be targeted solely at drugs and devices, for the same operational systems must manage the other 90% of imported shipments and the inspection of other products. The IT fix must either be across all Centers and ORA or it must occur at the Department level to leave open the option of breaking food regulation out of FDA and combining it with other food regulators into a Food Safety Administration as a sister to the remaining Drug & Device Agency.

Second, I recommend the establishment within FDA of an organization reporting to the Commissioner with the mission of focusing on enhancing the safety of imported products—all products. I continue to believe fixing FDA's import and foreign inspection problem requires it be broken free from the domestic programs, which produce much of the bureaucratic inertia against change in this area. A new organization would enable proper staffing, allocation of human resources at ports of entry, management and implementation of ISP-based strategies. It should be responsible for all import and international focused work-planning activities; conducting facility inspections of foreign processors and importers; overseeing and conducting border operations; conducting foreign government and industry assessments and training; and support trade negotiations in a manner to enhance safety of imported products. To accomplish this, the new organization should be directly funded, rather than receiving its funding through the product Centers. A basic persistent infrastructure to manage risks associated with all imported commodities must be maintained regardless of year-to-year changes that may appropriately occur in program directions.

Third, section 302(b) of the Bioterrorism Act, which enables FDA to implement risk-based strategies for managing food imports, should be expanded to cover all other FDA-regulated products including drugs. This would clarify FDA's authority to facilitate the importation of drugs that are in compliance with FDA requirements and pave the way for distinguishing between and among shipments based upon verifiable risk data.

Fourth, FDA should be required to inspect foreign drug facilities (at least those that fall into categories FDA admits should be inspected on a regular basis) at the same frequency as domestic facilities.

Fifth, FDA should work with Customs to adopt a uniform numerical identification system to begin the process of regulating its industries using an account-based system. This would enable FDA to integrate its numerous and disparate background data systems and to interrelate the data it receives from Customs and other government agencies.

Sixth, FDA should publish and begin implementing the ISP in accordance with the plan's guiding principles, goals, and themes.

Seventh, FDA should begin developing programs for obtaining as much information as can be obtained from as many reliable sources as the Agency can find regarding the cGMP compliance status and supply chain security programs of foreign drug facilities that are not inspected by FDA. This population of drug manufacturers will always exist, and simply saying it represents too many companies for oversight or too much data to digest is no answer at all. Additional risk data could come in the form of third party inspection and certification companies, accompanied by a robust auditing process on both sides of the border, by foreign inspectorates, or by other U.S. Government Agency inspections and information. All such data should be connected to the firm's unique identifier and incorporated into the account data to permit its assessment in light of other legacy and other agency data. I continue to hold to the view that obtaining and assessing all available risk data better enables FDA to (a) target its foreign and domestic inspections; (b) interdict and examine high-risk imported drug shipments (related to product safety); (c) follow up in the domestic market those shipments that proceeded through the border with inadequate inspections; and (d) facilitate imported drug shipments that are likely to have been manufactured in accordance with FDA's cGMP requirements. This would

permit the Agency to focus its most earnest import inspection and examination efforts on shipments representing known and unknown risks.

Eighth, FDA requires additional resources to conduct more foreign inspections and import examinations and to develop and publish meaningful Agency guidance relating to identifying and managing risks in the full life cycle of imported products.

Ninth, FDA should rely on Customs and Border Protection and the Department of Homeland Security (DHS) to manage security risks associated with FDA regulated imports. DHS' security programs should be expanded to incorporate product security risks (such as product counterfeiting and tampering) rather than focusing solely upon the security of in-transit cargo or inbound containers.

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I thank the Subcommittee Chair and Members for the opportunity to discuss these important issues and I look forward to answering any questions.

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Mr. STUPAK. Thank you, and thank you to everyone for your testimony today.

Mr. Hubbard, Mr. Nielsen, Mr. England, I believe you were here when the Commissioner testified. What would each of you—if you would just give me quick—what would you each do if you were the Commissioner? How would you come to address this issue? Give me the top 3 things you would do, starting with you, Mr. Hubbard.

Mr. HUBBARD. First you have got to know who is making our drugs and sending them to us. So you need registration. And I think you've mentioned that.

Mr. STUPAK. OK. A foreign vendor registration we were talking about.

Mr. HUBBARD. Everyone that is in the supply chain, all the way back to the pig—the pig farmer and his heparin. So at least we know who they are and where they are. That is, I think, number one. Second, you need to get over there and look at all the facilities and see what you find. Because we don't know now because we don't go there. And, thirdly, as I think these gentlemen have mentioned, you have got to have some sort of IT system to track it.

And there are many more things you need to do, but I would put those 3 things as sort of the sequential first things to do to begin to get a grip on this problem.

Mr. STUPAK. Mr. Nielsen.

Dr. NIELSEN. I do believe—I do believe IT has to be the first item, and there has to be funding. It is for the center. It is for the ORA. Coupled with that, I would say number two is functional organizational structure to deal with the issues at hand; and I do concur with what Ben said, that there does need to be a separate entity.

I also recommended that, in my written statement, that the foreign inspection oversight, the border operations, and oversight of the importers are all extremely related as far as risk; and I do believe a formation of an organization with the responsibility and funded and empowered will provide solutions that will work. And certainly funding is still a big issue, but the funding needs to be attached to very specific events with articulated outcomes or expected outcomes.

Mr. STUPAK. Mr. England.

Mr. ENGLAND. I think there are two levels. One is, what do you do in the instant event; and I think that the FDA is doing probably

the best they can in trying to figure out where this product came from.

Mr. STUPAK [continuing]. Heparin you mean?

Mr. ENGLAND. Yes, right. The specific heparin situation. I disagree entirely with the theory that the inspection couldn't have had a significant impact in preventing this. I mean, I think if we keep in mind that the inspection that we have now seen the 483 for occurred after the adverse events, and we still saw the conditions we saw. If FDA had been there prior to the adverse events during a pre-approval inspection, I'm inclined to believe that they would have seen a facility in even worse condition, in which case they would not have been in a position to be a source for this product.

Mr. STUPAK. Hang on. OK.

Mr. ENGLAND. So I think—I think that the foreign inspection component is absolutely critical, and it has been for years. I also think that because of the mandate that FDA has to inspect the domestic industry every 2 years, you end up—I think FDA ends up trying to reach that mandate to the exclusion of the foreign market where it doesn't have the mandate and that it tries to do the best it can.

Most of the foreign inspections, in reaction to the idea that, well, even some foreign inspections were conducted and yet there was still contaminated product that came from perhaps those facilities, those inspections were probably 2-day pre-approval inspections. The inspection we just saw at this facility regarding heparin was probably a 5-day, I believe, inspection, far more deep. In the United States, that would have been a 10- to 12- to 16-day inspection.

Maybe that is not necessary to find the appearance of a violation and prevent that product to come in, but I would agree that a 2-day inspection may not be able to produce this or to be able to find these kinds of problems. So I think inspections.

But if you don't have the IT, it really doesn't matter what you do. You can't put together a risk-based program. I mean, even Customs work, the integration with international trade data systems, the FDA still has to have data to bounce that data against. And without integration on the FDA side, you can go one place to get the data, but you can't really do much with it anyway.

Mr. STUPAK. We are going to have a hearing next week, actually, next Tuesday, on heparin.

I don't mean to belabor the heparin point, but, Mr. England, you brought up—and I think Mr. Melancon brought up, too—it is our understanding that this plant was never inspected, but Baxter did inspect it. Where is the corporate responsibility here or why would Baxter inspect it and we still have all these problems that were highlighted in the document that you indicated with the FDA inspection?

I mean, if we had had—if the FDA did inspections, would that also pressure Baxter then in this case to make sure that what they are doing as inspections are robust and complete and safe for the American people?

Mr. ENGLAND. First, I don't want to get into a liability question, because I just don't. I have not seen any of the documents on those inspections. I have no idea what the scope of the Baxter review was.

Mr. STUPAK. It is called response——

Mr. ENGLAND. I mean, the importer of a product has responsibility to ensure that the product they are importing is in compliance with U.S. law. In the case of an API, that means that they should have some—they should be able to make some assertions as far as the product having been manufactured in compliance with GMPs. That is from the Federal perspective.

Mr. STUPAK. If the government system broke down here because it was never in fact inspected and if the private company that is making the profit here broke down, the American people are truly just at risk then. I mean, there is nothing we can do other than a re-overhaul of the FDA.

Mr. ENGLAND. I believe—I believe that that is not an overstatement.

Mr. STUPAK. Mr. Nielsen, you're trying to jump in there.

Dr. NIELSEN. And coupled with that, as far as responsibility is, I do think there has to be a reevaluation of the good manufacturing and practice regulations. It is not a new topic for the Agency, for a rewrite of the drug GMPs.

Mr. STUPAK. Any idea last time that was rewritten, Mr. Hubbard?

Mr. HUBBARD. 2003. They are relatively new, but they're very general. They don't really deal with some of the problems that arise here.

Mr. STUPAK. OK. Dr. Crosse, we're focusing quite a bit on IT here with these questions I was asking. But yet on page 12 of your testimony you talk about the Foreign Vendor Registration Verification Program, and I was pressing the Commissioner to try to give us some kind of idea on when it is going to happen. And, in your testimony, FDA currently plans to award this contract of May '08, but yet you cite for an example the Agency has not yet established the criteria it would use to determine which establishments would be visited for verification purposes to determine how many establishments it would verify annually. Does it look like one of these things where the FDA is going to award a contract but yet not have the criteria before we even have the contract?

Dr. CROSSE. It is not clear to us. This is something that is very new, and it was difficult for us to get very much information about it. Our understanding yesterday, after we submitted this statement, is now that it has been pushed off to June but that they do still intend to move forward in trying to establish some program.

It is not clear to us what exactly is going to be done under this contract, whether they are going to perform onsite inspections of a certain proportion of facilities, how they are going to select those facilities, what is going to be involved in the verification, what information they're going to get beyond just is there a building there and do they manufacture drugs. It is really unclear at this point, and we were not able to get very many specifics from FDA about it.

Mr. STUPAK. And I think Mr. Nielsen or Mr. England mentioned the Shared Establishment Data Service. That all would have to be dovetailed into this, also, would it not? FDA needs to know about it, but Customs needs to know what is coming in and—what's coming in. Could you probably get the information quicker by going to

Customs? Because at least they know what is coming into this country.

Dr. CROSSE. It is not clear how this backtracks to a particular facility that is manufacturing a drug. The information that is coming in from Customs is again—sometimes they have difficulty linking back in that way. And as I said in my statement, there is not yet agreement that this SEDs system, the unique identifier that would be used with Customs, is going to move forward, because it requires the agreement of a large number of Federal agencies, and they all have to fund the changes to their systems to make this work.

Mr. STUPAK. My time is running out, and I think we'll probably go a second round, because I enjoy this panel, and you have good suggestions.

But, Dr. Cassell, if I may, on page 56 of the Science Board report there is a recommendation—and I pressed the FDA last time and never got a commitment. So let me ask it this way. There is a recommendation that the FDA develop a comprehensive plan that includes how and when the Agency would respond to the recommendation.

Has anyone from the FDA, after you submitted a report, got back with the Science Board and said, here is what we're trying to do. Help us implement. Here are our recommendations to implement—I mean, you gave them a blueprint on how to fix things. Have they worked with you to try to get it implemented or say here is our priorities? What happened after you submitted your report?

Dr. CASSELL. To my knowledge, they have not gotten back to the Science Board. I'm only one member of the Science Board. They could have talked to others to share with us specifically how they would propose to implement their recommendations.

I'm aware, however, they have begun the review of ORA and NCTR that we have recommended, and I am aware that a chief scientist has been appointed, although that was not in relationship to our recommendation but, rather, it seems the PADUFA legislation that also recommended the chief scientific officer.

Outside of those three things, I'm not aware of other activities that are ongoing.

Mr. STUPAK. And as the chair of the Science Board, your Science Board members are available to help the FDA implement these recommendations, are they not?

Dr. CASSELL. Well, I'm not a chair of the Science Board, but, rather, I was chair of the subcommittee that conducted the review. But just, still, a member of the Science Board. But the Science Board clearly is eager to help in any way.

Mr. STUPAK. Mr. Shimkus for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

I, too, want to commend the chairman for the hearing and this panel in particular.

This has been held up maybe before. This is the hearing record from the 105th Congress, which is my first Congress, Volume III, 11 years ago. Far be it from us 11 years from now when someone goes through and holds this up that we haven't done this.

I liken this to—one of my other responsibilities was telecommunications and interoperability for first-line responders. We

have had Katrina. We've had September 11th. We're still—yes, we are still struggling, and we're trying to move. But, you know, people's lives are at risk, and so I—you all have been a great panel.

If everybody was living by the golden rule or the second table of the law and loving their neighbor and not wanting to steal, we wouldn't have this problem. But we live in a sinful world, so—but the folks that are producing illicit drugs to enter our consumer market, we ought to identify them. They ought to be punished to the full extent. Why can't we just say, you don't comply with our inspection regime, you don't sell in our country?

Mr. HUBBARD. Well, that is one of the things that I think is mentioned in Chairman Dingell's bill. The concept is, for both food and drugs, is if someone can't show that they are meeting our standards, they ought not to be sending us food, and the FDA ought to have the ability to say, did this company demonstrate that it met the standards? And if the answer is no, it doesn't come in. And then you've shifted the burden from FDA to find the problem back to the producer to show he is doing a good show.

Mr. SHIMKUS. Yes, I'm not a big—I'm not well received by the trial lawyers, but I'm thinking if they had some good ones in China, we may not have this problem sometimes because they would be going after these firms that are illicitly putting other elements in these drugs and taking advantage.

There are a couple parts of the testimony that we found compelling and—talk about. One of the questions this deals with, if we don't have institutional reform in the FDA and we just give them more money, what would be the result, do you think, Mr. Nielsen?

Dr. NIELSEN. Probably a little more of the same. Until there is a real change in direction in how resources are allocated, how priorities are selected—for example, I don't think it is just an issue of getting more resources, but there has to be a hard look as to how existing resources are also used. Even if the entire domestic industry is being inspected at the total expense of lack of oversight of the foreign supply just does not make sense.

Mr. SHIMKUS. Mr. England, do you want to chime in?

Mr. ENGLAND. Yes. I think that to a certain extent—I can give you just a couple of examples. I wish I brought slides with me.

Because if you look at the organizational structure of the FDA—you know, when the act was established in 1906, nobody imported anything in here. So the imports regime was set up under a curtain context which doesn't exist anymore.

And similarly, as time went on to the 1900s, there was some functionality in FDA for managing import issues. But most of what was coming in was bulk ingredients that was for further manufacturing. In those circumstances, FDA would ensure that there was inspection and quarantining that was happening on the domestic side and that they were properly qualifying—properly qualifying the vendors. So they'd use the domestic inspection.

Now we have a whole lot less of that. Now, in the drug industry, it is actually still very much like that, which is an example, for instance, with heparin, which is why you still have to do inspections of those bulk facilities.

But—so now you've got—you've got a situation where FDA has a division of import operations and policy that Carl was the direc-

tor over, and he is responsible for managing OASIS, the IT system. He has absolutely no authority over anybody in the field. He cannot tell them to do anything. So he can have all the great ideas in the world to fix a situation, but he lacks the power to make FDA move.

And those are the kinds of organizational structures that exist. It is an appendage. It is an appendage.

Mr. SHIMKUS. Let me follow up, because you all sat in to hear the Commissioner and his testimony, and my opening statements talked about how well-intentioned individuals go into the bureaucracy trying to slay the dragon and really walk away not being able to do so. I think there are more examples of that occurring than really transforming. Because some of the terminology—we talked about stovepipe and silos. I mean—and in my opening statement, a comment was if you were to just rebuild, I mean, stop and restart the process, how would we go about getting to that area of where we need to be?

So the question is, based upon listening to the Commissioner, did you get a feeling that there was an understanding of the transformational nature, that the FDA has to change, or did you get a feeling—I think the frustration is that it is not a 100 percent commitment.

Mr. England?

Mr. ENGLAND. Yes. I don't want to characterize the commitment level. I think, though, however, that part of it is that we are at a stage I think now where the Agency is saying what a number of us have been saying for literally a decade as far as this risk and these kinds of things that are out there. And they are starting to say it. But I also think that FDA has lost a fair number of people who actually would have known how to do it. So they are in some ways a little bit perplexed as to what the steps ought to be.

Also—I also feel that they feel pressure from Congress and from this committee and other committees perhaps that they should be doing certain things because it was mandated, even if maybe those aren't the best things to be doing. So I think they are a little bit between a rock and a hard place.

But I also would add that it does take more—we are way beyond strategy, way beyond planning, that the Agency should be assessing, OK, what can we not do right now in order to do these things that are priority and start this shift.

Mr. SHIMKUS. Part of stovepipe—and this may be just a couple of panelists. It is not directed to anybody. Whoever wants to chime in. Address the frequency debate both—obviously, we can't talk about frequency if we're not inspecting overseas. If we were, what would be the frequency there versus the frequency here?

You're talking about—Mr. England just mentioned mandated things that we have to do and may be—and my previous with the Commissioner talking about, you know, if a manufacturing facility has a 10-year record of being inspected every year with zero defects, shouldn't we consider frequency evaluation in that venue?

Anyone want to chime in real quick? Mr. Hubbard.

Mr. HUBBARD. Well, I think as a start you do need the same frequency. But I think Commissioner von Eschenbach was correct in that, over time, you do want to move towards a risk-based system.

If you've got a facility, as you say, that has been doing very well and makes a relatively low-risk drug, then maybe that gets a pass every 2 years; and someone who is not doing a good job or makes a high-risk drug gets inspected every year.

But they can't even begin that shift without resources, in my view. They would have to strip inspectors out of domestic inspections to fund anything foreign at this point, And then we could see the deterioration of our domestic drugs. So it is kind of——

Mr. SHIMKUS. I want to tie into the flexibility of domestic inspectors. I understand that. We get that there needs to be more resources but also the flexibility of being able to move an inspection regime and the frequency debate with international concerns.

Mr. HUBBARD. Well, that raises a whole other issue. Because they are having difficulty finding enough people willing to go to these countries. I think the Agency would like to create a foreign inspectorate of people that are hired for that purpose, posted in these countries and in sufficient numbers to do the coverage. And I think that is a good idea personally.

Mr. SHIMKUS. Go ahead, Mr. Nielsen.

Dr. NIELSEN. I would also say that that is another scenario where the integrated IT function is critical. You can gather all of this information, but you just as well not have it if you can't get access to it.

Mr. SHIMKUS. That's right. And I wanted to move—Mr. England, I just want clarification, and I think it ties in with IT. You propose what is called the accounting system approach. Can you just again for the—elaborate just for someone who is simple-minded, how is that a change?

Mr. ENGLAND. Yes. An account-based system, an account-based approach, as opposed to a transactional approach. Right now, if you look at the way FDA manages its import program, for instance, everything is on a line-by-line basis. Now, sometimes they will make some decisions based upon history of a processor. For instance, I would presume, based upon the warning letter, that this manufacturer of heparin is now on an import alert. Now, whether that works or not is a completely different question, because I think the import alerts don't work anyway in far too many cases. But, ordinarily, the Agency is doing transaction by transaction; and the inspector or the evaluator is trying to figure out whether to let this one in rather than—for instance, on a registration basis, someone registers, they—if there is a user fee, there is a user fee.

Mr. SHIMKUS. Do you think the FDA can do that now? Does it need legislative authority? Can they—can that be part of the change in dynamics?

Mr. ENGLAND. I think they could do it now. I would be surprised if they didn't have the authority to move to that system. They probably don't have the resources to do the IT piece of it, but I don't see an authority problem with it.

Mr. SHIMKUS. Thank you, Mr. Chairman. My time has expired. I appreciate your——

Mr. STUPAK. Mr. Melancon for questions.

Mr. MELANCON. Thank you, Mr. Chairman.

Mr. Hubbard, has there been—and I have only been here in the Congress for 3 years now. Has there been a period in time some-

where where, appropriation-wise, the Department was given some monies because of the concern with inspectors, that money was taken and then used other places? I have heard rumors of that, and I don't know if——

Mr. HUBBARD. Well, the best example is, after 9/11, HSS Secretary Thompson was very concerned about foreign products in general from a bioterrorism point of view, and with a lot of pushback from the White House, he demanded the hiring of new inspectors for the ports. And FDA very rapidly hired 650 new inspectors in 2003, hired them in a matter of weeks and trained them and had them going very quickly. The subsequent budget cuts, though, took away all those inspectors; and now they are actually back with fewer than they had before 9/11. So all those 650 folks are gone.

Mr. MELANCON. And they were just—instead of maybe trying to keep them on and then retraining them for foreign——

Mr. HUBBARD. There was no money to pay them. So they—it really wasn't that people were fired. It was an attrition. As inspectors retired or left, they couldn't—so they just disappeared over about 4 or 5 years.

Mr. MELANCON. Now, that was—I wasn't sure what the scenario was. I just heard that there were fewer people than there were at certain periods as of 9/11.

You mentioned in your testimony that China had been associated with a number of problems related to counterfeiting and tainted exports. Should the FDA consider treating the country's products, particularly in areas we have seen problems such as drug exports, different than other countries who have not advanced—who have more advanced regulatory systems, i.e., should we be focusing on China specifically?

Mr. HUBBARD. I certainly think that less-developed countries need inspection, at least an initial inspection.

One concept that we looked at a few years ago was to say that if a country or given product from a country was repeatedly problematic then that would trigger a greater degree of regulation so that that country would then have to come to the FDA and say we fixed whatever problem you found; future shipments to the United States will meet your standards and demonstrate that. And that would mean that countries that don't have a problem, that don't send bad products wouldn't have to do anything different. But countries with a problem, they would have to step up.

Personally, I think that concept is one that could be valid. But I think it is partly met by Chairman Dingell's bill through the certification concept.

Mr. MELANCON. So the tainted food, the toothpaste, the fish, what have we done? Have we just slapped their wrist and moved on?

Mr. HUBBARD. The way the law works now is FDA has to catch each shipment, find the problem and say you can't come in. Since they only inspect 6/10ths of 1 percent, very little gets caught. So you need to shift it the other way and say they need—the ones that are caught, they need to do something more. Because you know it is just going to keep on happening until they fix the problem.

Mr. MELANCON. In other words, if you start embargoing those products that have problems, then either the people that are importing or the people that exporting would start having a concern?

Mr. HUBBARD. That is exactly right. You need to put that burden back on them so it costs them money to keep sending bad food or bad drugs to us. Right now, it is just a cost of doing business because FDA catches so little.

Mr. MELANCON. Yes. Go ahead, Mr. England.

Mr. ENGLAND. If I could, just briefly. And I agree with those ideas in concept. The problem with it if we only go that direction is that you're right back to a transactional mode because you've got to figure out as those goods come to the United States which ones are the ones that are subject to the ban. You're still in that—which is still an IT issue, A.

And, B, it seems to me that if the FDA were to be able to do more foreign inspections, they would be able to better distinguish segments of industries and segments of—or kinds of industries in contrast to others and actually incentivize, for instance, in China, industries that are doing it right in order to create examples even in China.

And I think that is a kind of a policy that encourages a holding up of those that are meeting our standards rather than just trying to catch—I think we're still trying to catch them at the border, and I don't think it is going to be as effective.

Mr. HUBBARD. I agree with that. I don't think what I said—I think you need both, you know.

Dr. NIELSEN. And just a little clarity. The way the law is written right now for the admissibility—Bill had said it is up to the Agency to find the problem. It is not like USDA where there is an existing permit requirement that affirms compliance. And one of the possibilities with an account base is to be able to link. In order to establish an account is to have an affirmative process for that compliance.

Mr. MELANCON. Is it your opinion in having similar problems or countries within the union like we're having with imports coming in that are tainted?

Mr. HUBBARD. Well, certainly they have had a problem with heparin. Germany has already had several deaths. And just today I understand Spain has announced heparin adverse reactions. So it can go anywhere. And, as the FDA said yesterday, there are about a dozen countries that have gotten contaminated heparin.

Dr. CROSSE. I would just add also that the EU doesn't do as many inspections of the active pharmaceutical ingredients, the API manufacturers like the facility in China. So they are less likely to be doing those inspections.

I would also point out it is not a simple matter to just say this country's products that are coming to the U.S. could be problematic, because those products go other places and then come to the U.S. For example, China ships many products to the EU to be incorporated in finished products that are manufactured there and then come to the U.S. So the chain can go many directions.

Mr. MELANCON. And, of course, I deal with shrimp because I'm from south Louisiana. I understand that most of the shrimp that are aquaculture-type shrimp or—that might be sent to the EU, get

discovered to be bad and where do they end up? They end up here, I believe, if I'm not mistaken. So our own FDA isn't protecting us on that foodstuff.

Mr. England, Mr. Hubbard and Mr. Nielsen, shouldn't we require a hefty registration fee for those foreign establishments to ensure that if a firm is going to register at the FDA they are serious about exporting to the U.S. market? Would that help clean up the foreign drug inspection database?

Dr. NIELSEN. I think it can help, but I believe what is more important is the link with the registration process, a requirement to provide affirmative information that they can make the product in conformance with FDA requirements. Even if they didn't ship but they provided information that if they did ship, it could be significant information. Even if they are distributing somewhere else on the globe but they ultimately intend to be here, there could be some utility. But the bottom line is we need much more information than just who they are. We need to know what the conditions are, can they make a safe product.

Mr. MELANCON. And that is kind of one—the point is, what do we do to make them know up front that we are going to be checking or that we want—we are going to be on top of it? I mean, is there any specific recommendation?

Dr. NIELSEN. I would modify the registration process. The current registration process—and, as Bennett said, establish a universal process for all of the commodities. But that process was just totally inadequate. It is not just an IT issue. You and I can register right now. OK? No problem.

Mr. MELANCON. What does it cost me?

Dr. NIELSEN. Nothing. You can go online and do it.

Mr. MELANCON. Fill out the form?

Dr. NIELSEN. That's right. But the bottom line—that is just very cursory information. To make real risk-management decisions, you need to know something about the operation. Are they capable, even if it is the basics. And I think the registration process should be more of a submission of more information or develop some kind of process that will be recognized by the Agency as verifying that this place does exist, that it does have potable water, et cetera, whatever the infrastructure is required for safety.

Mr. MELANCON. Is there anywhere in this process bond that are required of any of these folks that register or do importing into this country? I.e., if I'm an insurance company and I'm going to write a bond for you, I want to know damn well that what you are shipping in that country I'm not going to have to pay off on that. Do we require anything such as that?

Mr. ENGLAND. Not for registration. There is a bond for every importation. It is a basic importer's bond, and it is usually for FDA purposes, FDA products, three times the invoice value. So——

Mr. MELANCON. So how—OK. It is three times the invoice value of that one shipment.

Mr. ENGLAND. Right.

Mr. MELANCON. But if we don't have the authority to go embargo every other pile that is coming in——

Mr. ENGLAND. Well, I mean, at this point, they have the authority to detain without physical examination any shipment. And

that's where you get to the—for instance, the countrywide import alerts that we have for the wheat gluten and the soy proteins and aquaculture coming out of China. Those are countrywide import alerts. And the Agency does them now.

I think part of the question—I mean, the question about whether the Agency has the authority to refuse has to do with whether or not if someone delayed or denied an inspection in a foreign facility, then FDA could automatically put them up into an automatic detention and stop their products. But FDA has the authority to do that now.

I think the reason it is not doing them is that—Carl hired the guy who is running policy at DIOP now. They have 5 people, I think. I mean, the people who are responsible for OASIS and responsible for reviewing import alerts, there are 5 people doing it, and we are talking about 17 million lines of entry that these folks are responsible for.

That goes to resources. It goes to IT. It also goes to theory and policy and where you put the resources. And I don't think many people are really thinking about it inside the Agency, because they're just trying to do what they have always been doing and that is what—that's why I believe the series of events are really just beginning, that we are going to see a series of these from a number of different sources.

Mr. MELANCON. Thank you. My time is up and this—Mr. Chairman. Go ahead.

Mr. STUPAK. Go ahead, Doctor. Do you want to answer this question?

Dr. CASSELL. Yes. I would just like to say that, to me, it all goes back not only to the resources and priority setting but people and the quality of individuals now, that we don't have good people there.

We mentioned in our report the importance of constant external peer review that would identify these problems, make an argument for correcting them, stay on top of them before we have an emergency. ORA, for example, we identified had never had an external peer review. So this review that is ongoing right now, it is the first time to our knowledge that has ever occurred. I think a lot of these problems would not have occurred had those processes been in place.

I just wanted to bring to the attention of everybody that I think that the issue of personnel is critical—getting the right people, recruiting them, retaining them, whether it be the scientists or information technology specialists, which they seem to have a hard time recruiting, are absolutely critical to everything we are talking about today.

Mr. ENGLAND. I would like to follow up, if I could, please.

I agree absolutely, entirely. When I say resources, I mean humans as well, human resources. And I'm going to give you just an example.

When the Office of Criminal Investigations came online in 1992, I went into OCI. I was one of the early agents that came out of FDA and into OCI. And OCI was responsible from really that point forward in conducting criminal investigations and conducting investigations that where there is some suspicion of fraud—CSOs,

the Consumer Safety Office, or the inspectors, they only started losing those skills.

I mean, many folks that used to do the investigations were conducted by the regular inspectors. And now, once you had a criminal enforcement arm, they began to—the inspectors began to just have to check boxes off. And they—and I think that there was a training—some training that was lost. I think there was some intelligence that was lost. Not that they are not intelligent, but as far as institutional knowledge about how to think through these situations like the drug investigations where just a keen investigator knew how to do investigations and he was an inspector and he put 2 and 3 together, came up with the number 5, pulled in people, got resources. And at one point we had 10, 12 grand juries running. And so it can be done.

But I think that that part goes to the organizational aspect of it. These inspectors can do it with the tools. If they have the tools and they have the training and they have the time to be in the facilities, they can do it.

Mr. STUPAK. We would have a second round of questions, but go back to OCI. On Ketek, the OCIs were doing their job, and they were asked to do their investigation, and they were denied the opportunity. And they got frustrated and basically are leaving the Agency because they're not allowed to do their work in some cases. It is more of a structural thing.

And we were talking of issues of mandates that the FDA—we—this committee or our Energy and Commerce Committee, we don't mean to micromanage the FDA on—mandate lots of programs. But without quality of leadership at the top of the FDA, we must resort to mandates as a trigger or a triage or emergency patch to correct some of these most pressing issues.

And that's why I was pressing the Commissioner today on BPA or on discussion draft of the legislation we have floating. Because we want to move that quickly to try to give them the resources they need to do their job and to help reconfigure the FDA so we can get at this issue, which is getting to be a growing problem.

Along those lines, on our legislation, Mr. Hubbard has mentioned—and a couple of the others have mentioned it—if you have some suggestions on things we should improve upon in that draft, we are moving on that bill fairly quickly. So if you have anything further, please get with us.

Dr. Cassell, you indicated new drugs, new biologics, the genome, that active pharmaceutical ingredients, other things we were going to be relying upon, given the multitude of additional foreign firms—and you're going to see places like Thailand, Vietnam and Malaysia are expected to start making drugs and will likely export to the U.S. If we're grappling with a problem right now and all these other countries come on line and new medical discoveries come online, how are we ever going to be able to keep ahead of the curve?

Dr. CASSELL. Oh, I agree. I think in some respects it is almost mind-boggling when you think about the degree of the complexity of the products increasing and especially in terms of safety issues as it relates to biologics. They are not as easily manufactured as you—we all know and appreciate as small molecules. So I think,

again, it goes back to assuring that we have the latest scientific evidence for the decisions that would be made, the best people making those decisions, the technologies in place to improve upon our inspections.

We mentioned in our testimony, I think, in some of the discussion on the 29th of January that the Department of Defense, Department of Homeland Security has invested millions of dollars in their information technology for doing datamining in a lot of different topics, particularly as it relates to biological weapons, and they have also developed very sophisticated methodologies for detection in the field of both chemicals and biologicals. These same methodologies could be applied, I believe, to inspection in terms of quality control as far as potential chemical and biological contamination of our products.

I don't know to what extent the FDA has tried to leverage those technologies and apply them or bring them on line, but I think we have to begin to apply newer, better technology as well as just be sure that the individuals that are performing these functions are up to date in terms of what new science is available to help resolve the problems.

Mr. STUPAK. In the last panel, we talked a little bit about this heparin and the altered drug, and I think Mr. Burgess brought up the fact that it could have been for a criminal or a deviant mind. But whether it is melamine or heparin, I don't think we see that.

Is it really economic pressures putting pressure on to find a cheaper substitute? As in melamine, you know, it was supposed to be high protein, but it ended up—why would you alter a drug? Does anyone care to speculate on that? I'm sure it is just not criminal. I mean——

Mr. HUBBARD. You have very good chemists over there. And the best example is pharmaceutical grade glycerin is fairly pricey, and antifreeze you can get down at the dollar store. So, you know, it tastes the same; it looks the same. It is just one will kill you, and one is perfectly safe. And, you know, people just don't care about where it ends up going. And, of course, a lot of children in Haiti and Panama and other countries die because someone didn't care.

Mr. ENGLAND. I think also, if I could quickly, that my understanding was that there was a problem with some of the——

Mr. STUPAK. The pig intestines. The pig stock, right.

Mr. ENGLAND. So they were running into a capacity problem. So it wouldn't surprise me that, under that pressure, that there was some intent to find something to put it in there.

I'll point out, just quickly, the APIs that FDA approved—and everything goes into a source inspection and finds an API facility to be fined, the value of their product on the world market doubles overnight. So, right now, you've got the incentive, you've got cushion between guys who are—people who are not approved and people who are. And it is a lot cheaper sometimes to buy the product than it is to make it.

Mr. STUPAK. So instead of using the pig intestines and heparin and I use something else, do I have to get FDA approval to make heparin in this manner and method or can I just say, oh, no, this is OK because the end result is still heparin?

Mr. HUBBARD. You're supposed to get approval. But, believe me, you can get it for that.

Mr. STUPAK. Is that common? I mean, we make substitutions to a formula that we use?

Mr. HUBBARD. You can't do that. You have to at least—it depends on the severity of the change. If it is a very great change, you have to get FDA approval. If it is a minor change, you have to at least tell FDA so they can object.

Dr. NIELSEN. I mean, one of the things to keep in mind, even on the counterfeit APIs, like the carbamazepine, it has to pass the test. Even if it is nominal, it has to pass the identity test at least. And so it has—it is going to have to look like that or else at least the safeguard at the end user or the finished dose manufacturer will detect it.

Mr. STUPAK. Mr. England, you mentioned the import alerts. In fact, as this panel was seated, we've had three import alerts just come out from the FDA on some foods and other issues here. You're not a big fan of it. They don't work, you said. Explain that a little bit further. And what should we do?

Mr. ENGLAND. Right. I mean, what solutions perhaps there might be as far as them not working, I think that is an IT issue. There is evidence last year where products that were—that should have been subject to a number of different seafood a reporter rather quickly found 200-some-odd shipments that had gotten through the system and had never been tested by the FDA and had never been stopped, even though they were subject to the criteria.

So when Carl was asked in the press as to whether or not that surprised him, of course the answer is no. I mean, there has been holes in that system forever. So putting up an import alert is not an answer. It certainly is a piece, and it certainly does put information out there.

I think another aspect of it is that I'm not so sure that the FDA has the authority that it exercises sometimes in these countrywide alerts. So if Congress wants FDA to have that, that is something they may want to consider clarifying. But, in many respects, the import alert is supposed to be just guidance to the field, and it really ends up acting as a regulation.

And I think that is where the Agency begins to run into some potential liability. They've been challenged a number of times, and I don't think they have—I don't think FDA has won yet when they've been challenged on an import alert as to whether it was legitimate. To fix that—those sort of problems, I think FDA——

In fact, Bill Hubbard, when he was in the Agency and along with us, we went through a process of trying to establish what we called a detention without physical examination rule that basically described these are the kinds of evidence the FDA might rely on to issue an import alert. Here is the kinds of evidence we might seek in order to overcome it. And at least you created a regulatory regime to manage it, and then your guidance could be your alerts that are just applying the reg.

But there is a number of those kinds of situations, both IT—and I think also the way that the authority is structured, that the Agency is vulnerable, and it is not as effective.

Mr. STUPAK. Let me just—and anyone can jump in on this one. But, Mr. Hubbard, it is more directed at you.

I'm not a big fan of PADUFA, where you have a user fee that gets your drugs approved with the new drug applications. But, from a practical point of view, PADUFA has worked. I mean, you've given them money. The drugs are approved by such and such a time line. I'm not talking about the safety or efficacy of it, but we've met those timelines, given the resources.

And I know Mr. Burgess kept bringing up the tobacco issue. Again, they will be given the resources. If given the resources, with a clearly defined mission, can the FDA—and the Dingell bill, Dingell-Pallone-Stupak bill—we have a registration fee that is probably going to be sizeable to fund this program. Can the FDA do the job if given the resources in a focused area as in PADUFA or tobacco regulation? Wherever there might be—as long as resources are there and they—can they attract the science people that we need to do the job in this country?

Mr. HUBBARD. I think absolutely. I think the programs in a more funded FDA work well. You don't hear the criticisms about them. And the programs that are not funded well are the ones that everyone is screaming about.

The one problem with PADUFA is that it is sent to the OMB and the appropriators. There is a lot of new money flowing into FDA. So we can cut back on appropriations. And those cutbacks have occurred in places like imports and food safety, not in the drug-review programs. So it has had a negative consequence, I'm afraid, in that sense.

Mr. STUPAK. Sure. And in that sense, like the new money coming into the FDA in the last budget, that is really from MADUFA and PADUFA fees. There is really not that much new money to take care of these shortfalls, and that's what we've got to guard against.

But it seems like the $71 million we've been talking about to do the proper inspections is probably a small amount; and we can attract the science and the inspectors we need, provided we have a dedicated funding source. Because I don't want to see an example like this panel has pointed out where Homeland Security had the 650 inspectors, got them right away right after 9/11, got them trained and within 2 or 3 years they were all gone because there was not a dedicated funding source. That seems——

Dr. Cassell, do you want to jump in on that?

Dr. CASSELL. I think you're right to be concerned about that. I, like Mr. Hubbard, though, believe given the resources with emphasis upon the right people, not just warm bodies, I think they can absolutely do the job.

The other thing that I would just encourage us all to think about again, though, is to encourage putting in place this external peer review, if you will, process. Because, to me, that would also help ensure accountability. And in the long run I know it is just one more committee for FDA to deal with. But if you look at the NIH, if you look at CDC now, they have these external review committees in place. The peer pressure does play an important role in keeping things on track.

Mr. STUPAK. My time is up.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Again, I appreciate the panel. I, too, am adverse—Federal Government, we always overpromise; we underdeliver. If we set up a trust fund, we all dip into it. So we—I think this legislation would have a much better success if it was a Dingell-Pallone-Stupak-Barton deal and Shimkus. Maybe we will get there.

Because there are a lot of things that we agree upon and, hopefully—I know the legislation is out for comment. Hopefully, our folks—I'm going to check with Barton and Diaz and see what they think of it.

I also thought about the current—well, it's an old series of books and movies: Series of Unfortunate Events. And we don't want this to continue to be a series of unfortunate events. Everything does go back to leadership, though. I mean, I'm from the military school of training, and someone at the top has to drive transformational change. And that we are all skeptical——

And it goes back—it is not one—Commissioner von Eschenbach has only been there 2½ years. Now that 2½ years really makes substantial changes, but there was guys before him. There will be folks after him. There is other administrations. And we have fallen to a dilemma that a lot of us don't want to see. We want to see it fixed.

And I think you've got some great comments. You talked about—Chairman Stupak talked about if other countries start coming into the system. I wish legislatively we could stop—if you're in a hole, the best way to get out of it is to stop digging. We have got new entries into this. Maybe that is where we start a regime. But then you have not being favorably inclined to——

Mr. England, do you want to chime in on that?

Mr. ENGLAND. Yes, just quickly, because this actually came up early; and I don't know if I forgot to answer it or left it for somebody else.

But the question is to whether or not—what is the point about why are we going to China in order to try to do MRAs? Why are we trying—probably 50 percent—Carl probably knows the number better than I do—of what is imported either comes from Canada or Mexico or comes through Canada and Mexico. And they are right here. They are our NAFTA neighbors. We have access to them. We have ways to put together risk-based programs, and we can actually verify it.

I mean, my feeling is that if we were to focus where we could apply risk-based principles and be able to have some verification, trust but verify, and then you take the resources and you put them where you really don't have any basis to trust or verify, then I think you start creating incentives for countries to want to be those countries and they want to be like those countries. And you throw in the registration pieces and expenses of that and where that money goes I think is important.

I think, you know, your IT money and how that is applied is a management decision. But when it comes to this, how you address China versus other places, I think we have got—we actually have the ability to show some leadership in markets where we have access to show it, prove it and then begin to create the incentives for other countries to come into it.

Mr. SHIMKUS. I want to go back to the account-based with a question. Have you—or anyone might—I think everybody understands the premise. Is there anything that the FDA is doing right now that gives you hope that they are understanding that or moving in that direction?

Mr. ENGLAND. I would have to see what the current IT proposals are. My recollection of the IT proposals as I left and the ones I saw from November were—mostly was a portal overlaying existing systems. Which means you still have your silos. You just have them in one basket now.

Mr. SHIMKUS. What—let me jump—predict that we have all been waiting—is that—would that—if that was taken hold of and moved, would that be moving in that direction?

Mr. ENGLAND. PREDICT would require integration to be most effective. But PREDICT itself is not an integration system. What it does do, though, is take data from multiple sources; and it does think about that data using evolutionary algorithms. But it also uses it with rules based looking at the Agency's historical data. So it is hard to go from seafood into other products without already having—being able to do some of that risk analysis to think about how you're going to weight, you know, these different characteristics. So it will not do the integration, but I think it should be at the front end of their inspection program as well. I mean, I think it just makes the most sense.

Mr. STUPAK. If I can jump in for just a minute. You know, I sat through the '98 hearing when J.L. testified again about the IT system, and it has been 10 years. Why is IT here such a problem to get our hands around? It is not just FDA. It seems like IT just seems to be a problem that the government can't get its hands around, especially this one. We have got I think seven different databases we are dealing with the FDA on food and drug safety. Why has this been an insurmountable task that we can't seem to get to?

Dr. NIELSEN. From my observation, a good portion of the existing legacy system is based on the need of a particular product center. And ORA is not directly funded, and IT is not directly funded. And that is why one of my proposals is—why I believe a new entity, funded entity needs to be established, is you have to start line item the IT. And ORA set it in the position, doing a good portion of the post-market surveillance work, what need for information from each of those silo legacy systems. It has to be integrated.

The investigators and ORA either at the border or doing facility inspections need information. They are going to go from one industry to another. They may do a drug inspection, a device inspection, a biologic inspection. So that is why the integration. But it is not funded. It is just—it is not a direct line. And ORA considerations, in my opinion, just have not been at the fore.

Mr. HUBBARD. If I may, Mr. Chairman, the IT is expensive. The Science Board suggested it needed about $800 million. And I think the folks at—above FDA have just not felt that it is worthy. And, in fact, many years we would ask for money—around the time of your '98 hearing, we were asking for money for import IT. In fact, we would get cuts that said you don't really—IT, that is not important. You can always use efficiencies and do better. And it

squeezed—it cut 10, 20 million. And so you have never had that commitment to fixing the IT systems. So you have these 1970s and '80s systems limping along, totally ineffective.

Mr. STUPAK. Dr. Cassell.

Dr. CASSELL. Yes. I would agree and just remind you in our report we pointed out that FDA's IT budget is less than half of that that CDC currently has, yet the information that needs to be managed is far greater.

The other thing I have heard this week that is very disturbing is that, while we were well on our way to developing a new IT system for adverse event reporting, apparently the backup system that we pointed out that didn't exist actually doesn't exit. It was lost. They are 6 weeks behind in terms of implementation, and the problem still hasn't been resolved. So I think again this is one area that is urgent. It is critical that it be fixed and fixed quickly.

Mr. HUBBARD. Can you imagine the frustration at FDA last year when the FBI decided its $800 million system didn't work and threw it away and said we'll start over. Now, if they had gotten that kind of money, I personally think FDA would have spent that.

Mr. STUPAK. Mr. England, go ahead.

Mr. ENGLAND. Just real quick examples. One—because I think some of this responsibility actually happens because Congress sometimes tries to fix problems one piece at a time. Prior notice, for example. FDA got mandated—you were mandated to do due prior where they were given no money to put the IT system together. So all the money they were going to use for OASIS enhancements all went into prior notice, which, quite frankly, I think didn't really accomplish very much.

Now, as we think about the idea of proposing a registration system where people pay money for registration, some of that money will go into what? An IT system. And it will be a stovepipe system just like the rest of them. So as these solutions come up, if they're not for across the entire agency, it actually aggravates the problem. They start using that money to create stovepipe solutions to manage the new mandate.

Mr. SHIMKUS. Yes, and that's one of the issues of the whole institution; and, indeed, if you would rebuild it from the ground up—and we've got to break down these barriers.

I'm going to throw out 3 phrases for the sake of time and just have comments.

The appearance standard for kicking off an import alert and then also the debate on extraterritorial jurisdiction on our ability to hold overseas importers somehow more accountable under the law. Any comments on that? Does that make sense? I mean, I can go into the whole question, but you know the phrases, right?

Mr. ENGLAND. The appearance standard, I mean, right now the Agency already has the authority under the appearance standard. Nobody knows what it is. No judge has ever said so, nor will the FDA ever want a judge to say so, because they would all of a sudden have a standard that they would have to meet. But there is no—the appearance standard—as long as it appears to be in violation of the act, they can stop that product now.

And then the courts tend to defer to the Agency as to what the appearance is. And is that right? Well, I represent other people who don't like that, but you can see why judges do it.

As far as extraterritorial power, you're not really reaching into those foreign governments with that standard. All you're doing is—you're just saying, not in my backyard, not here.

Mr. SHIMKUS. I know that the question is should that be something that we legislatively consider?

Mr. HUBBARD. The appearance standard is a relic of 1906. It says the FDA has to define either that problem clearly or the appearance of that problem and then stop the product. If you're going to change the paradigm, you need to move the burden to the producer to show they are making safe food or drugs, not on FDA to find every single problem with every single shipment when you have 20 million shipments.

Mr. SHIMKUS. Mr. Nielsen.

Dr. NIELSEN. I think the task is to make certain it is equal burden for the domestic and foreign industry or else it is unfair competition.

Mr. ENGLAND. I mean, just on the extraterritorial question, I would think—it would seem to me where it would be difficult is how you enforce it. I mean, if—and part of it—if you're talking about some how penalizing——

Mr. SHIMKUS. I understand—I mean, we were talking about heparin a lot, but if there is criminality——

Mr. ENGLAND. The United States government already has power to prosecute foreign nationals that commit those kinds of crimes. They've done it before. They did it in the drug investigations. Gerd—what is his name? Gerd Weithase was a German national. He was involved in the manufacture—somehow involved in the scheme——

Mr. SHIMKUS. You know, I'm getting help here, but I hear that DOJ wants some explicit language to help us more fully prosecute.

Mr. ENGLAND. DOJ has often gone along with FDA and said we agree. That would certainly help. It isn't clear that the Food and Drug Cosmetic Act—and I think that clarification was not going to hurt anything.

Mr. SHIMKUS. But if we are moving legislation, if we wanted it clear, we could at least look at the language.

Mr. HUBBARD. FDA would clearly like you to deal with the extraterritoriality.

Mr. SHIMKUS. Thank you. I'm done, Mr. Chairman. Thank you.

Mr. STUPAK. Mr. Melancon? No.

Well, thank you to this panel. It is always a very, very good panel. We enjoy it. That's why I like the members to just go on and ask the questions.

I mentioned the three recalls just while this panel was empaneled. We had from China snow fungus, which is mushrooms; from Vietnam, ginger; and from China, dried lily bulbs. Those are three recalls—or alerts that just came in.

Mr. ENGLAND. Not my clients——

Mr. STUPAK. I thought I'd give you a heads-up.

Mr. NIELSEN [continuing]. Yet.

Mr. STUPAK. I am still trying to figure out what do we do with dried lily bulbs.

Anyway, that concludes our questioning. I want to thank our witnesses for coming today and your testimony and thank you again. And, Dr. Cassell, be sure you tell your committee thank you very much for their work and expertise.

I ask unanimous consent that the hearing record will remain open for 30 days for additional questions for the record.

Without objection, the record will remain open.

I ask unanimous consent that the contents of our document binder be entered in the record.

Without objection, documents will be entered into the record.

That concludes our hearing. Without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 3:00 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

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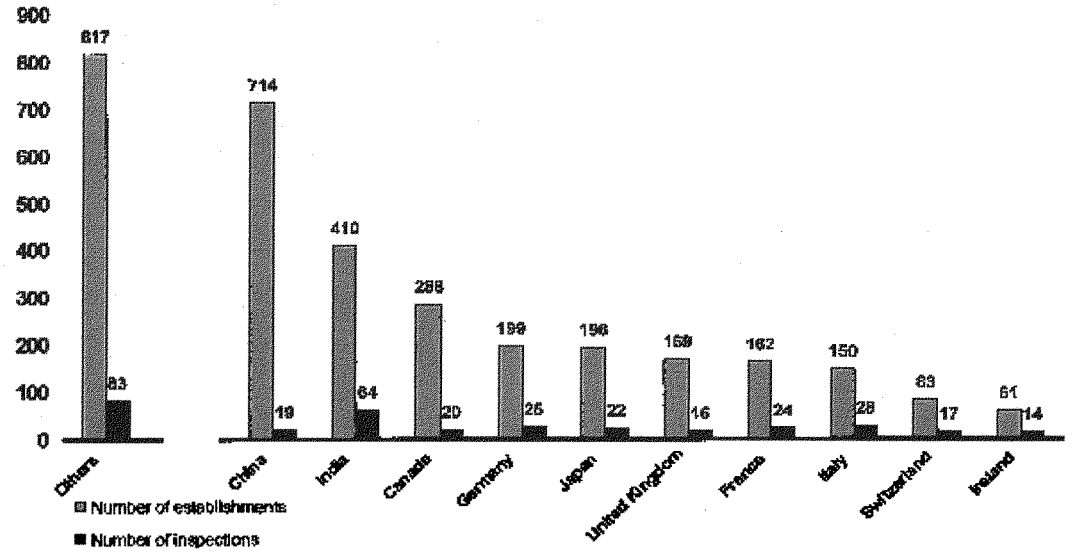
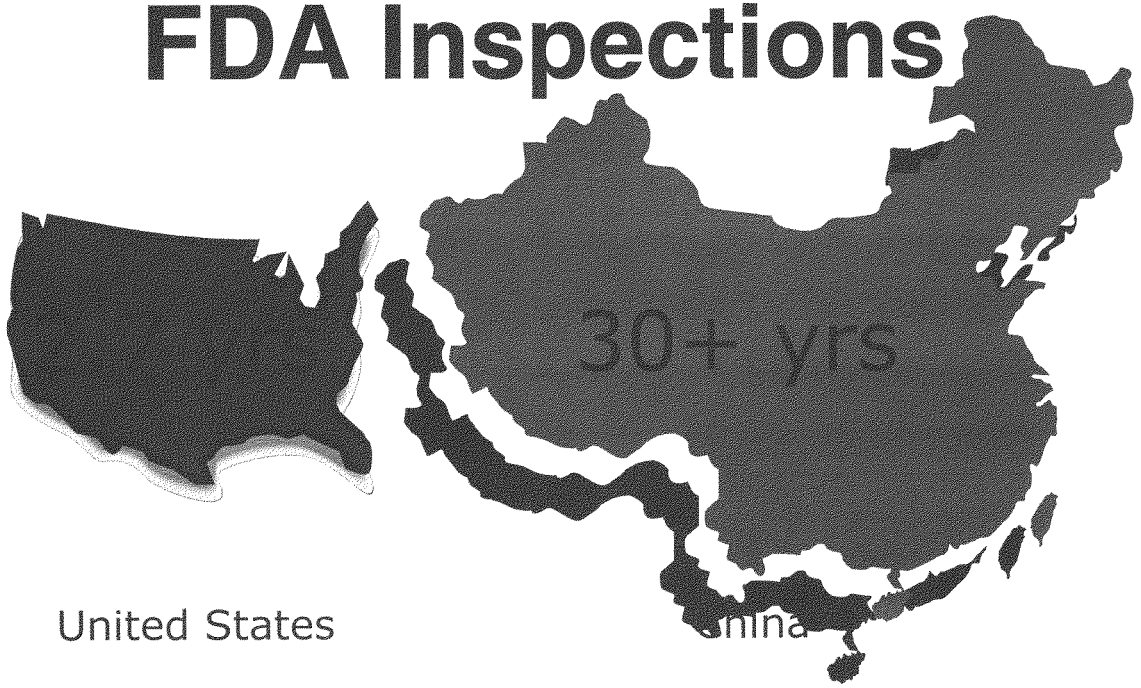
# Number of Foreign Establishments and FDA Inspections, including for the 10 Most Frequently Inspected Countries, Fiscal Year 2007

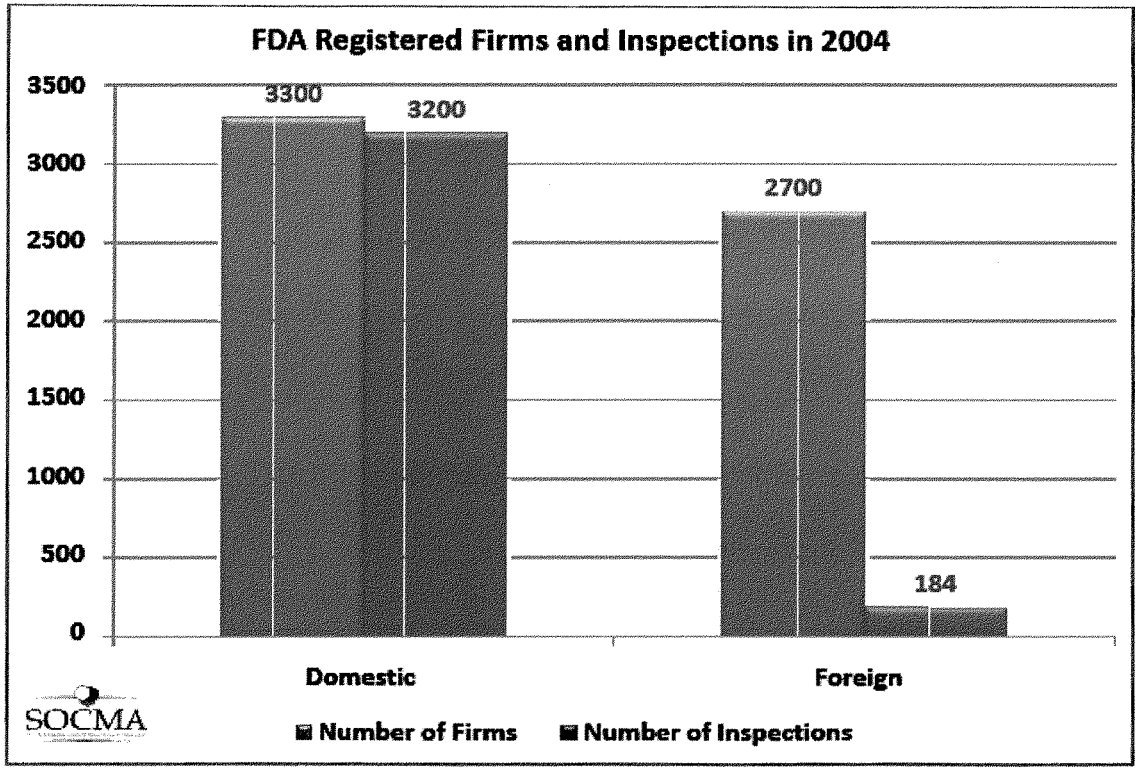



Source: GAO analysis of FDA data.

# Average Time Between FDA Inspections

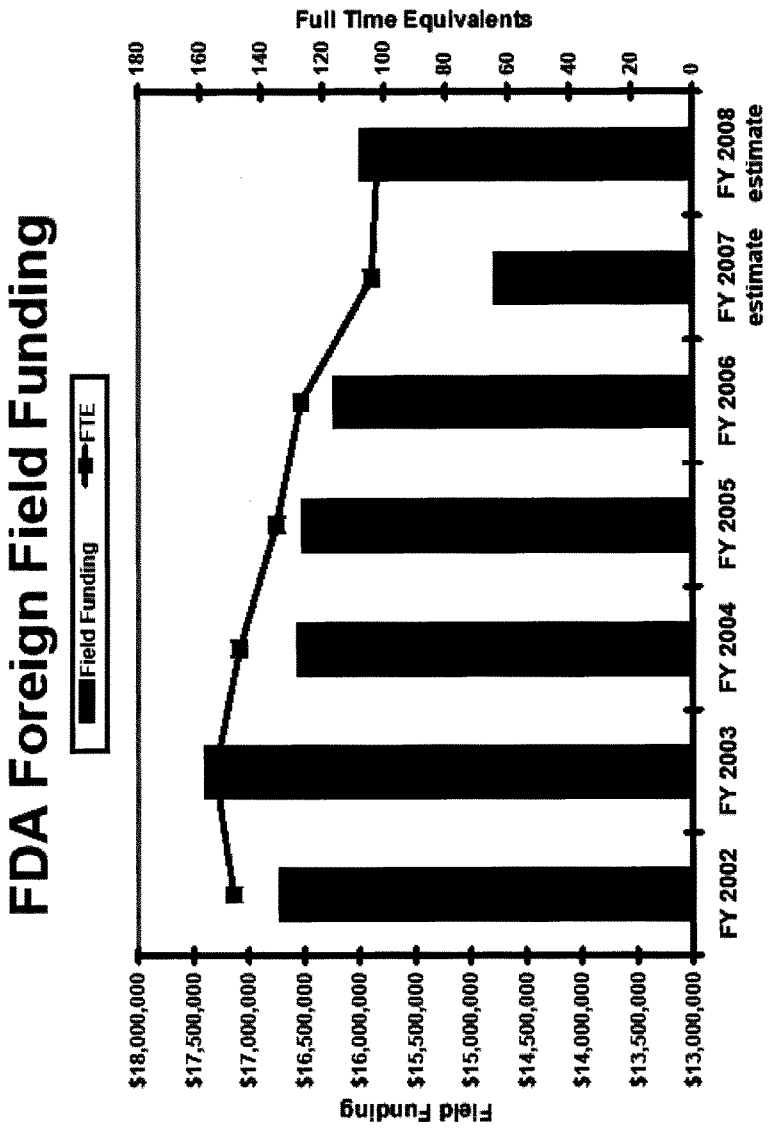



Source: GAO/HEHS-98-21 Foreign Inspection Program




Number of firms data taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 29th International cGMP Conference, University of Georgia, March 2005.

Number of inspections data taken from the 2004 CDER Report to the Nation published August 2005.




*FDA Data Provided to Committee on Energy and Commerce, October 2007

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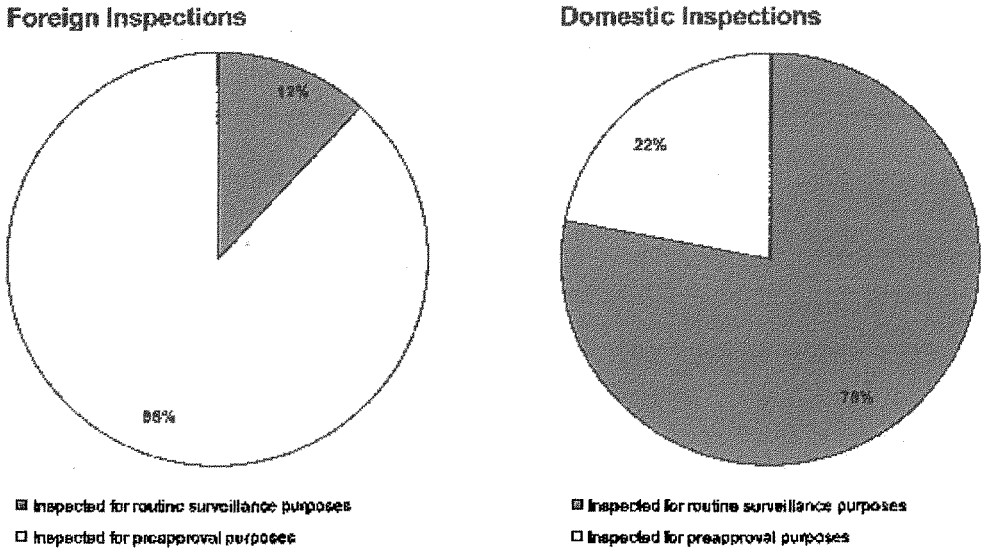
# Foreign and Domestic Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007




Source: GAO analysis of FDA data.

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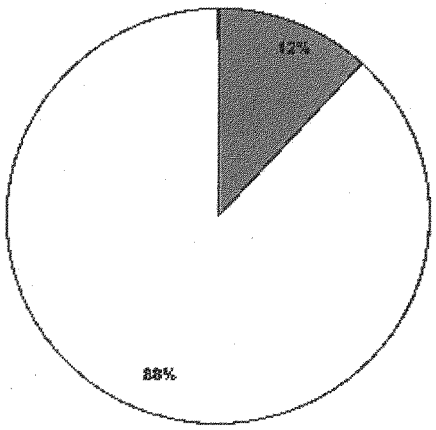
# Foreign Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007

**Foreign Inspections**




- Inspected for routine surveillance purposes
- Inspected for preapproval purposes

Source: GAO analysis of FDA data.

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# FDA Data Used to Estimate the Number of Foreign Establishments Subject to Inspection

**Drug Registration and Listing System (DRLS):**

- Contains information on about **3,000** foreign establishments registered to manufacture drugs for the United States.
- FDA does not routinely verify the information provided by establishments.

**Operational and Administrative System for Import Support (OASIS):**

- Contains information showing that about **6,800** foreign establishments had drugs imported into the United States.
- OASIS may artificially inflate the number of foreign establishments.

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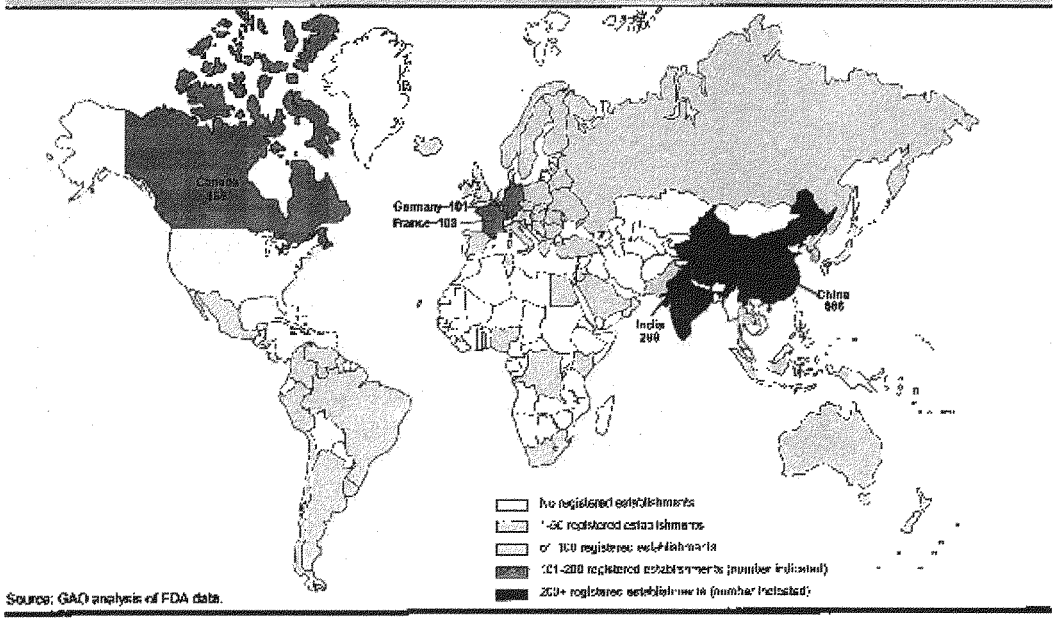
# Foreign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007




Source: GAO analysis of FDA data.

| # | Description | Date |
|---|---|---|
| | | |
| | | |
| | | |
| 1 | GAO Testimony from 11-1-2007 Oversight and Investigations Subcommittee hearing. | 11/1/07 |
| 2 | GAO Testimony from 1-29-2008 Oversight and Investigations Subcommittee hearing. | 1/29/08 |
| 3 | Slide Presentation | |
| 4 | New York Times article by Walt Bogdanich and Jake Hooker, re: "China Didn't Check Drug Supplier, Files Show." | 2/16/08 |
| 5 | New York Times article by David Barboza and Walt Bogdanich, re: "Twists in Chain Supplies for Blood Drug." | 2/28/08 |
| 6 | New York Times article by Gardiner Harris and Walt Bogdanich, re: Drug Tied to China Had Contaminant, FDA Says." | 3/6/08 |
| 7 | New York Times article by Walt Bogdanich, re: Heparin Find May Point to Chinese Counterfeiting." | 03/20/08 |
| 8 | New York Times article by Walt Bogdanch, re: "Heparin Is Now Suspected in 62 Fatalities Across U.S." | 4/10/08 |
| 9 | Wall Street Journal article by Gordon Fairclough, re: "How Heparin Maker in China Tackles Risks." | 3/10/08 |
| 10 | Wall Street Journal article by Anna Mathews and Thomas Burton, re: "FDA Identifies Contaminant in Heparin Batches." | 3/20/08 |
| 11 | FDA Warning Letter to Changzhou SPL Company, Ltd | 4/21/08 |
| 12 | Associated Press article, re: "The Head of the FDA Says His Agency Simply Could Not Handle the Massive Funding Boost that Outside Advisers Say it Desperately Needs." | 04/15/08 |
| 13 | New York Times article by Gardiner Harris, re: "Panel's Bipartisan View: FDA is Underfinanced." | 04/16/08 |
| 14 | Washington Post article by Marc Kaufman, re: U.S. and China Dispute Conclusions About Tainted Heparin." | 4/21/08 |
| 15 | Chicago Tribune article by Bruce Japsen, re: "FDA: Heparin Supplier's Chinese Factory 'Unsuitable'." | 4/21/08 |
| 16 | Bloomberg article by Justin Blum, re: "U.S. and China Clash Over Cause of Heparin Deaths." | 4/21/08 |
| 17 | Wall Street Journal article by Jacob Goldstein, re: "FDA Points Finger at China on Heparin Once More." | 4/21/08 |
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United States Government Accountability Office

GAO

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

For Release on Delivery
Expected at 10:00 a.m. EDT
Thursday, November 1, 2007

# DRUG SAFETY

# Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

Statement of Marcia Crosse, Director
Health Care


GAO-08-224T

November 1, 2007

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# Highlights

Highlights of GAO-08-224T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

## DRUG SAFETY

## Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

### Why GAO Did This Study

Many drugs marketed in the United States are manufactured in foreign countries and the value of such products entering the country is increasing. The Food and Drug Administration (FDA) is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments. Foreign establishments that market their drugs in the United States must register with FDA and FDA inspects foreign establishments to ensure that they meet the same standards that are required of domestic ones. GAO reported 9 years ago that FDA needed to improve its foreign drug inspection program (GAO/HEHS-98-21). Questions remain as to whether FDA has improved its management of the foreign drug inspection program.

This statement discusses preliminary information on (1) the extent to which FDA has accurate data to manage the foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections. To address these issues GAO interviewed FDA officials; reviewed pertinent statutes, regulations, and guidance; and analyzed information from FDA databases. Because of the preliminary nature of our work, we are not making recommendations at this time.

To view the full product, including the scope and methodology, click on GAO-08-224T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

### What GAO Found

FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its databases. FDA does not know how many foreign establishments are subject to inspection. Instead, FDA relies on databases that were not designed for this purpose. Further, these databases contain inaccuracies that FDA cannot easily reconcile. One database indicates there were about 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while another indicates that about 6,800 foreign establishments actually imported drugs in that year. FDA recognizes these flaws. Further, because the databases cannot exchange information, any comparisons of the data are performed manually, on a case-by-case basis. FDA officials told GAO that they have not generated an accurate count of foreign establishments whose drugs are imported into the United States.

FDA inspects relatively few foreign establishments. Data from FDA suggest that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection. However, FDA cannot provide an exact number of foreign establishments that have never been inspected. Most of the foreign inspections performed are conducted as part of a review associated with processing an application to market a new drug, rather than inspections for monitoring the quality of marketed drugs. Although FDA uses a risk-based process to develop a prioritized list of foreign establishments for inspections to monitor the quality of marketed drugs, few are completed in a given year. This prioritized list was used to select foreign establishments for inspection in fiscal year 2007. According to FDA, about 30 such inspections were completed in that year and at least 50 are targeted for inspection in fiscal year 2008.

The foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections to monitor the quality of a marketed drug, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you examine the Food and Drug Administration's (FDA) inspections of foreign drug manufacturers whose products are imported into the United States. In 1998, we reported that FDA needed to improve its foreign drug inspection program.[1] Among other things, we noted that FDA had serious problems managing its foreign inspection data and that it lacked a comprehensive automated system for tracking this important information. We were also critical of the number of inspections FDA conducted at foreign manufacturers. At that time, FDA reported on our growing dependence on imported pharmaceutical products, noting that as much as 80 percent of the bulk drug substances[2] used by manufacturers in the United States to produce prescription drugs was imported and that the number of finished drug products manufactured abroad for the U.S. market was increasing. Today, we are still dependent on foreign establishments[3] manufacturing drugs for the U.S. market as the value of pharmaceutical products coming into the United States from abroad continues to increase.[4]

Given the importance of FDA's foreign drug inspection program, you expressed concern about FDA's ability to oversee foreign establishments manufacturing drugs and asked whether FDA has improved its management of the foreign drug inspection program since our previous report was issued. My testimony today will summarize preliminary findings from our ongoing work to update our 1998 report. My remarks will focus on (1) the extent to which FDA has accurate data to manage its foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections.

[1]GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: Mar. 17, 1998).

[2]A bulk drug substance is any substance that is represented for use in a drug that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished drug product. 21 C.F.R. § 207.3(a)(4)(2007).

[3]FDA regulations define an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.3(a)(7)(2007). Drug firms may have more than one establishment.

[4]According to GAO analysis of International Trade Centre data, the value of pharmaceutical imports increased 42 percent from 2001 to 2005 adjusted for pharmaceutical inflation. The International Trade Centre is a joint agency of the United Nations Conference on Trade and Development and the World Trade Organization.

To address these issues, we interviewed officials from FDA's Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign drug inspection program. We reviewed pertinent statutes and regulations as well as agency documents that provide guidance on conducting inspections and provide the basis for FDA's assessment of an establishment's compliance with current good manufacturing practices (GMP).[5] These documents included FDA's Compliance Program Guidance Manuals, its Guide to Inspections of Foreign Pharmaceutical Manufacturers, and its Investigations Operations Manual 2007. We also obtained information from FDA databases on establishments whose drugs have been imported into the United States. Specifically, we obtained data from the Drug Registration and Listing System (DRLS), the Field Accomplishments and Compliance Tracking System (FACTS), and the Operational and Administrative System for Import Support (OASIS). We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them, (2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of data elements from FACTS. We found the data in the FACTS database reliable for our purposes. We also found that DRLS was reliable, to the extent that it accurately reflects information provided by foreign establishments that register to market drugs in the United States. However, we determined that these data do not necessarily reflect all foreign establishments whose drugs are imported into the United States. In addition, we found that OASIS is likely to over-estimate the number of foreign establishments whose drugs have been imported into the United States, due to uncorrected errors in the data. Therefore, we present information from both DRLS and OASIS to illustrate the variability in information that FDA's databases provide to agency officials on this topic. This represents the best information available and is what FDA relies on to manage its foreign drug inspection activities. Our ongoing work is focused on human drugs regulated by CDER and not on biologics,[6] medical devices, veterinary medicines, or other items or products for which FDA conducts inspections. We received technical comments on a draft of this statement from FDA, which we incorporated as appropriate.

[5]GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality products. See 21 C.F.R. pts. 210, 211 (2007).

[6]Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Some biologics are regulated by CDER and inspections related to those products are included in our work.

Our work is being performed in accordance with generally accepted government auditing standards.

In summary, our preliminary results indicate that more than 9 years after we issued our last report on this topic, FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its data systems. FDA does not know how many foreign establishments are subject to inspection. FDA relies on information from several databases that were not designed for this purpose. One of these databases contains information on foreign establishments that have registered to market drugs in the United States, while another contains information on drugs imported into the United States. One database indicates about 3,000 foreign establishments could have been subject to inspection in fiscal year 2007, while another indicates that about 6,800 foreign establishments could have been subject to inspection in that year. Despite the divergent estimates of foreign establishments subject to inspection generated by these two databases, FDA does not verify the data within each database. For example, the agency does not routinely confirm that a registered establishment actually manufactures a drug for the U.S. market. However, FDA used these data to generate a list of 3,249 establishments from which it prioritized establishments for inspection.

Because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. We found that FDA inspects relatively few foreign establishments. Using the list of 3,249 establishments from which FDA prioritized establishments for inspection, we found that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment on this list once, assuming that no additional establishments are subject to inspection. FDA cannot provide the exact number of foreign establishments that have never been inspected. Most of the foreign inspections are conducted as part of processing a new drug application (NDA) or an abbreviated new drug application (ANDA),[7] rather than as GMP surveillance inspections, which are used to monitor the quality of marketed drugs. Although FDA used a risk-based process to develop a prioritized list of foreign establishments

[7]FDA must approve an NDA in order for a new drug product to be marketed in the United States; approval for a generic drug is sought through an ANDA. FDA also reviews scientific and clinical data contained in these applications, as part of its process in considering them for approval to be marketed.

for GMP surveillance inspections in fiscal year 2007, few such inspections are completed in a given year. According to FDA, about 30 such inspections were completed in fiscal year 2007 and at least 50 are targeted for inspection in fiscal year 2008. Further, the data on which this risk-based process depends limits its effectiveness.

Finally, the very nature of the foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA does not have a dedicated staff to conduct foreign inspections and relies on those inspecting domestic establishments to volunteer. While FDA may conduct unannounced GMP surveillance inspections of domestic establishments, it does not arrive unannounced at foreign establishments. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult to conduct than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Because of the preliminary nature of our work, we are not making recommendations at this time.

## Background

FDA is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments.[8] Foreign establishments that market their drugs in the United States must register with FDA. As part of its efforts to ensure the safety and quality of imported drugs, FDA is responsible for inspecting foreign establishments whose products are imported into the United States. The purpose of these inspections is to ensure that foreign establishments meet the same manufacturing standards for quality, purity, potency, safety, and efficacy as required of domestic establishments.

Requirements governing foreign and domestic inspections differ. Specifically, FDA is required to inspect registered domestic establishments

[8]FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. See 21 C.F.R. § 207.3(a)(8) (2007).

that have been previously approved to market their drugs in the United States every 2 years,[9] but there is no comparable requirement for inspecting foreign establishments. FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to conduct physical inspections of the imported product or prevent its entry at the border.

Within FDA, CDER sets standards for and evaluates the safety and effectiveness of prescription drugs and over-the-counter drugs. Among other things, CDER requests that ORA inspect both foreign and domestic establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including current GMPs. CDER requests that ORA conduct inspections of establishments that produce finished drug products. CDER also requests inspections of those that produce bulk drug substances, including the active pharmaceutical ingredients (API)[10] used in finished drug products. These inspections are performed by investigators and laboratory analysts.[11] ORA conducts two primary types of inspections[12]:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug product. Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications and ensures that the manufacturer of the finished drug product, as well as each manufacturer supplying a bulk drug substance used in the finished

[9]21 U.S.C. § 360(h).

[10]An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product.

[11]ORA investigators lead inspections. They are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing.

[12]FDA may also conduct other postapproval inspections, such as to address adverse events associated with a particular drug. In addition, FDA conducts for-cause inspections when it receives information indicating problems in the manufacture of approved drug products, as well as when it follows up on manufacturers that were not in compliance with GMPs during previous inspections.

product, manufactures, processes, and packs the drug adequately to preserve its identity, strength, quality, and purity.

- Postapproval GMP surveillance inspections are conducted to ensure compliance with applicable laws and regulations pertaining to the manufacturing processes used by domestic and foreign establishments in the manufacture of finished drug products marketed in the United States and bulk drug substances used in the manufacture of those products. These inspections focus on a manufacturer's systemwide controls for ensuring that drug products are high in quality. Systems examined during these inspections include those related to quality control, production, and packaging and labeling. These systems may be involved in the manufacture of multiple drug products.

FDA allocates funds to ORA to carry out preapproval and postapproval inspections of foreign and domestic establishments. ORA develops an annual work plan and a budget that estimates human resources available to conduct activities related to foreign inspections. ORA also develops estimates for inspections of domestic establishments. Typically, ORA investigators and laboratory analysts travel abroad for about 3 weeks at a time, during which they inspect approximately three establishments. Each establishment inspection typically lasts a week, with 1 day of each week set aside for documenting the inspection or for extending the inspection, if necessary.

CDER uses a risk-based process to select some domestic and foreign establishments for postapproval GMP surveillance inspections. According to an FDA report,[13] the agency developed the process after recognizing that it did not have the resources to meet the requirement for inspecting domestic establishments every 2 years.[14] The process uses a risk model to identify those establishments that, based on characteristics of the establishment and of the product being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. (See table 1 for a description of the risk-based site selection model

[13]Department of Health and Human Services, U.S. Food and Drug Administration, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model," (September 2004), http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm (accessed Oct. 21, 2007).

[14]Previously, FDA used other less formal risk-based systems to prioritize its inspections. For example, we noted in our 1998 report that FDA had used a risk-based site selection system, in which it classified establishments according to risk tiers. See GAO/HEHS-98-21.

used by FDA in fiscal year 2007.) For example, FDA considers the risk to public health from poor quality over-the-counter drugs to be lower than for prescription drugs, and consequently establishments manufacturing only over-the-counter drugs receive a lower score on this factor than other manufacturers. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments. CDER began applying this risk-based process to domestic establishments in fiscal year 2006 and expanded it to foreign establishments in fiscal year 2007.

**Table 1: Summary of Factors in FDA's Risk-Based Site-Selection Model in Fiscal Year 2007**

| Category of factor | Description | Example(s) |
|---|---|---|
| Product | Factors pertaining to the intrinsic properties of drug products such that quality deficiencies could potentially and adversely affect public health | FDA considers establishments manufacturing prescription drugs, as opposed to only over-the-counter drugs, to be higher risk |
| Process | Factors pertaining to aspects of drug manufacturing operations that may predict potential difficulties with process control or vulnerability to various forms of contamination | FDA considers establishments manufacturing small-volume drugs administered intravenously to be higher risk than those manufacturing prompt release tablets, because of the greater risk of contamination associated with the manufacture of small-volume intravenous products |
| Facility | Factors relating to characteristics of a manufacturing site believed to be predictive of potential quality risks | FDA considers establishments that have not had a recent GMP inspection to be higher risk than those that have received a recent GMP inspection |

Source: GAO analysis of FDA's risk model.

FDA relies on multiple databases to manage the foreign drug inspection program. FDA assigns unique numeric identifiers to establishments, known as the FDA establishment identifier (FEI) number. An FEI number could be assigned at the time of registration, importation, or inspection.

- DRLS contains information on foreign and domestic drug establishments that have registered with FDA. Establishments that market their drugs in the United States must register with FDA. These establishments provide information, such as company name and address and the drug products they manufacture for commercial distribution in the United States, on paper forms that are entered into DRLS by FDA.

- OASIS contains information on drugs and other FDA-regulated products imported into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by U.S. Customs and Border Protection, which are originally entered by customs brokers based on the information available from the importer.[15] Each establishment is assigned a manufacturer identification number that is generated from key information entered about an establishment's name, address, and location.

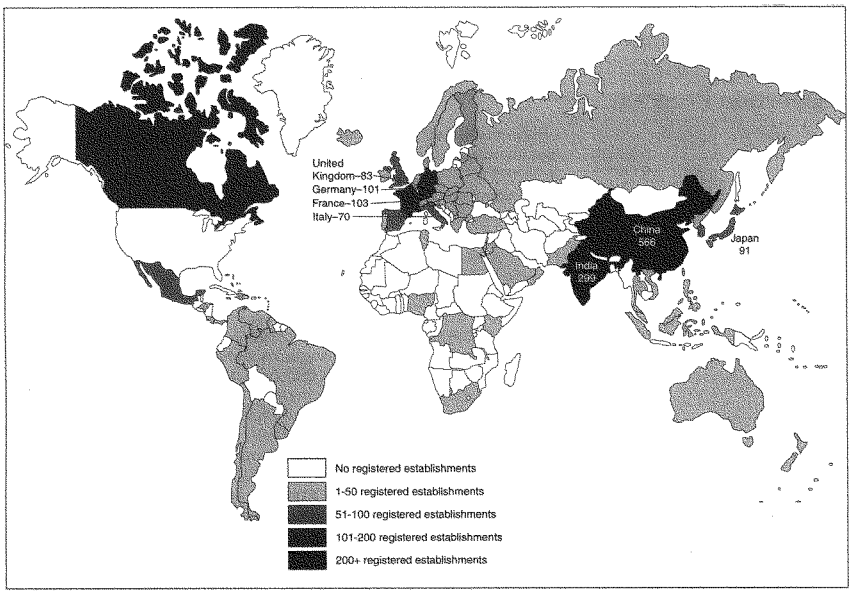
- FACTS contains information on FDA's inspections of domestic and foreign drug establishments. FDA investigators and laboratory analysts enter information into FACTS, following completion of an inspection.

According to DRLS, in fiscal year 2007, China and India had more establishments registered to manufacture drugs for the U.S. market than any other country.[16] Other countries that had a large number of establishments registered to manufacture drugs for the U.S. market in this year were Canada, France, Germany, Italy, Japan, and the United Kingdom. (See fig. 1.) These countries are also listed in OASIS as having the largest number of manufacturers importing drugs into the United States.

[15]Customs brokers are private individuals, partnerships, associations, or corporations licensed, regulated, and empowered by U.S. Customs and Border Protection to assist in meeting federal requirements governing imports and exports.

[16]These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

**Figure 1: Foreign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007**




Source: GAO analysis of FDA data.

Note: These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

## FDA Lacks Accurate Information to Effectively Manage the Foreign Drug Inspection Program

FDA does not know how many foreign establishments are subject to inspection; including the number of establishments that are registered and whose products are currently imported into the United States and establishments that are not required to register but whose products are ultimately used in drugs that are marketed here. Instead of maintaining a list of such establishments, FDA relies on information from several databases that were not designed for this purpose.

DRLS, established in 1991, is intended to list the establishments registered that manufacture drugs for the U.S. market. However, requirements for the registration of foreign establishments were not implemented until 2002.[17] FDA expected that requiring foreign establishments to register would provide it with a comprehensive list of such establishments. In fiscal year 2007, approximately 3,000 foreign establishments were registered with FDA that manufactured human drugs, biologics, or veterinary drugs; FDA was unable to determine from this database the number of registered establishments specifically manufacturing human drugs.

DRLS provides FDA with some information about establishments subject to inspection, but contains inaccuracies and does not provide a complete count. FDA officials told us that the count of registered foreign establishments in DRLS does not reflect the actual number whose products are being imported into the United States for several reasons. First, foreign establishments may register with FDA, whether or not they actually manufacture drugs for the U.S. market. FDA officials told us that this is made more likely by the fact that FDA does not charge foreign establishments a fee to register. FDA officials pointed out that some foreign establishments register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA. Second, foreign establishments may not renew their registration information, although they are required by FDA to do so annually. Agency officials told us that if foreign establishments stop manufacturing drugs for the U.S. market or go out of business they may not report the change to FDA, even though it is required. FDA officials told us that the agency does not routinely verify the information provided by the establishment to ensure that it is accurate or confirm that the establishment actually manufactures

[17]See Pub. L. No. 105-115, §§ 417, 501, 111 Stat. 2296, 2379-80. FDA issued implementing regulations in 2001, which were effective February 11, 2002. 66 Fed. Reg. 59138 (Nov. 27, 2001).

drugs for the U.S. market.[18] FDA does not know how many foreign establishments are erroneously registered. Third, foreign establishments that manufacture APIs are not required to register if their products are not directly imported into the United States.[19]

OASIS also provides FDA with some information about establishments subject to inspection, but this database contains inaccurate data on the count of foreign establishments manufacturing drugs imported into the United States. According to OASIS, 6,760 foreign establishments manufactured drugs that were imported into the United States in fiscal year 2007. However, FDA officials told us that errors in data entry result in inaccurate counts of establishments whose drugs are imported into the United States. FDA officials told us that if information about an establishment—such as its name—was entered by customs brokers incorrectly, a new manufacturer identification number, and thus a new FEI number, could be assigned to an establishment that already has an FEI number. For example, a customs broker may enter an establishment's name slightly differently from the way it is displayed in OASIS, such as using "Inc." instead of "Incorporated," which would lead to the creation of a second FEI number for the establishment. Therefore, a single establishment may be counted more than once in OASIS, which would result in an artificially high count of foreign establishments importing drugs into the United States. FDA officials acknowledge this problem but were unable to provide us with an estimate of the extent of that error. In addition, the agency does not have a process for systematically identifying and correcting these errors. To mitigate this problem, the officials told us that FDA has provided regional training to brokers as a way to improve accuracy. FDA officials also told us that the agency is pursuing a new government-wide initiative that would address this problem by providing a unique identifier for each foreign establishment involved in the import supply chain.

FDA's data suggest that between 3,000 and 6,760 establishments could be subject to FDA inspection. However, FDA officials told us that the two

[18]If the agency learns of an error, it would ask the establishment to submit corrected information.

[19]For example, an establishment in China may export an API to Germany. The German establishment may use the API in its production of a drug that is imported into the United States. Although the German establishment would be required to notify FDA of its arrangement with the Chinese establishment, and the Chinese establishment would be subject to inspection by FDA, the Chinese establishment is not required to register.

databases—DRLS and OASIS—cannot be electronically integrated or interact with one another, so any comparisons are done manually for each individual establishment. Because comparisons of the data and error identification are done manually, the databases are not conducive to routine data analysis. FDA officials told us that they have not generated an accurate count of the establishments whose drugs are imported into the United States.

Because FDA does not have a list of all foreign establishments subject to inspection, in fiscal year 2007 it created a list of such establishments for the purpose of applying its risk-based process.[20] In preparing this list, FDA draws on information from DRLS. It also obtains information from previous inspections to help it identify establishments that are subject to inspections but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. For fiscal year 2007, this list consisted of 3,249 foreign establishments. However, as a result of the inaccuracies in DRLS, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

[20]In addition to establishments identified for the purposes of conducting its risk-based analysis, FDA also identifies establishments subject to inspection that are named in NDAs or ANDAs using its Establishment Evaluation System database. This database identifies the multiple establishments involved in drug manufacturing, including the establishments manufacturing a finished product for import into the United States and the establishments manufacturing any APIs for that finished product.

## FDA Conducts Relatively Few Foreign Establishment Inspections and Relies on the NDA and ANDA Review Process as the Primary Selection Factor

FDA conducts relatively few inspections of foreign drug establishments. However, because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. Most foreign establishments are selected for inspection as part of the agency's review process associated with an NDA or ANDA. Therefore, the vast majority of foreign inspections include a preapproval inspection. In addition, although FDA has implemented a risk-based process in selecting foreign establishments for GMP surveillance inspections, relatively few such inspections are conducted. FDA tries to make efficient use of its resources by selecting establishments for these inspections that allow it to coordinate travel with preapproval inspections.

### Relatively Few Foreign Establishments Are Inspected by FDA Each Year

In each year we examined, FDA inspected a small portion of foreign establishments through either preapproval or GMP surveillance inspections. However, its lack of a list of foreign establishments subject to inspection makes it difficult to determine an exact percentage. Based on our review of data on inspections, FDA conducted an average of 241 foreign establishment inspections per year from fiscal year 2002 through fiscal year 2007.[21] Comparing this average number of inspections with FDA's count of 3,249 foreign establishments it used to plan its fiscal year 2007 prioritized GMP surveillance inspections suggests that the agency inspects about 7 percent of foreign establishments in a given year. At this rate it would take FDA more than 13 years to inspect this group of establishments once, assuming that no additional establishments are subject to inspection.

FDA's data indicate that some foreign drug manufacturers have not received an inspection, but the exact number of establishments not inspected was unclear. Of the list of 3,249 foreign establishments, there were 2,133 foreign establishments for which the agency could not identify a previous inspection. Agency officials told us that this count included

[21]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year. Our analysis includes all foreign and domestic inspections that were identified in FDA's data as being either related to the drug application approval process or GMP. It does not include a small number of other inspections, such as those related to problems identified by consumers or health care professionals.

registered establishments whose drugs are being imported into the United States that have never been inspected but also included other types of establishments, such as those whose products were never imported into the United States or those who have stopped importing drugs into the United States without notifying FDA. FDA was unable to provide us with counts of how many establishments fall into each of these subcategories. Of the remaining 1,116 establishments on FDA's list, 242 had received at least one inspection, but had not received a GMP surveillance inspection since fiscal year 2000,[22] and the remaining 874 establishments had received at least one GMP inspection since fiscal year 2000. Of these 874 establishments, 326 had last been inspected in fiscal years 2005 or 2006, 292 were last inspected in fiscal years 2003 or 2004, and the remaining 256 received their last inspection from fiscal year 2000 through fiscal year 2002.

FDA has increased the number of foreign establishments it inspects, most of which are concentrated in a small number of countries. From fiscal year 2002 through fiscal year 2007, the number of foreign establishment inspections FDA conducted annually varied from year to year, but increased overall from 222 in fiscal year 2002 to 295 in fiscal year 2007. During this period, FDA inspected establishments in a total of 51 countries. More than three quarters of the 1,445 foreign inspections the agency conducted during this period were of establishments in ten countries, as shown in table 2. The country with the most inspections during this period was India, which had 200 inspections. Inspections of establishments located in India increased from 11 in fiscal year 2002 to 65 in fiscal year 2007.

[22]According to FDA officials, some of these establishments may have received an inspection for another type of product, such as a veterinary drug.

**Table 2: Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Market, by Country for the 10 Most Frequently Inspected Countries, Fiscal Year 2002 through Fiscal Year 2007**

| | Number of inspections | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Country | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007[a] | Total | Number of establishments[b] |
| India | 11 | 19 | 38 | 33 | 34 | 65 | 200 | 410 |
| Germany | 24 | 15 | 35 | 25 | 19 | 22 | 140 | 199 |
| Italy | 17 | 30 | 26 | 21 | 18 | 19 | 131 | 150 |
| Canada | 29 | 12 | 17 | 23 | 23 | 19 | 123 | 288 |
| United Kingdom | 19 | 22 | 15 | 18 | 15 | 13 | 102 | 169 |
| France | 14 | 15 | 13 | 12 | 16 | 24 | 94 | 162 |
| China | 11 | 9 | 17 | 21 | 17 | 13 | 88 | 714 |
| Japan | 11 | 13 | 14 | 21 | 13 | 15 | 87 | 196 |
| Switzerland | 12 | 12 | 11 | 17 | 9 | 14 | 75 | 83 |
| Ireland | 11 | 5 | 11 | 14 | 3 | 11 | 55 | 61 |
| All other countries | 63 | 38 | 63 | 61 | 45 | 80 | 350 | 817 |
| **Total** | **222** | **190** | **260** | **266** | **212** | **295** | **1,445** | **3,249** |

Source: GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

[b]This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections.

## The Need to Conduct Preapproval Inspections Associated with NDAs and ANDAs Drives FDA's Selection of Foreign Establishments

While enforcing GMP compliance through surveillance inspections is FDA's most comprehensive program for monitoring the quality of marketed drugs, FDA's inspections of most foreign establishments occur as part of the agency's review of an NDA or ANDA. Agency officials said that FDA may need to inspect establishments involved in the manufacture of the drug referenced in an NDA or ANDA in order to meet specific goals for the timely review of these applications. As we reported in 1998 and we still found in 2007, most inspections of foreign manufacturers occur only when they are listed in an NDA or ANDA. For fiscal years 2002 through 2007, 88 percent of FDA's inspections of foreign establishments were conducted as part of the preapproval process. When FDA receives an NDA or ANDA, CDER officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the NDA or ANDA has received a satisfactory GMP inspection in the previous 2 years and the agency has no new concerns,

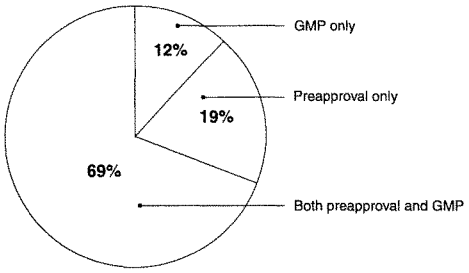
FDA will consider this inspection sufficient and will not perform a preapproval inspection of this establishment.[23]

FDA often includes a GMP inspection when it visits an establishment for a preapproval inspection. As presented in figure 2, from fiscal year 2002 through fiscal year 2007, the majority of FDA's foreign inspections combined a preapproval inspection with a GMP inspection. According to FDA officials, because foreign establishments are inspected infrequently, it is expedient for investigators and laboratory analysts to conduct preapproval inspections and GMP inspections during the same visit to a foreign establishment. During one establishment visit, FDA investigators can conduct inspections related to multiple compliance programs.[24] Because a GMP surveillance inspection examines the major manufacturing systems at an establishment, the results of such an inspection can be generalized to all products manufactured at a particular establishment. FDA can thus use the results of the combined inspection to make decisions in the future if that establishment is listed again in another NDA or ANDA.

[23]According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product.

[24]Compliance programs outline procedures for conducting different types of inspections, including preapproval inspections for drugs that are the subject of an NDA or ANDA, drug manufacturing inspections, and drug repacker and relabeler inspections.

**Figure 2: FDA Foreign Establishment Inspections by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007**

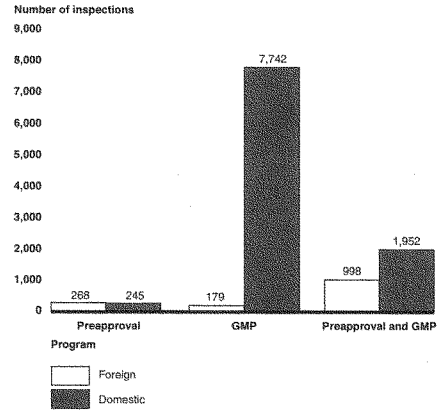



Source: GAO analysis of FDA data.

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA conducts fewer GMP surveillance inspections of foreign establishments than it does of domestic ones. Of the 1,445 foreign establishment inspections conducted from fiscal year 2002 through fiscal year 2007, 1,177 inspections included a GMP component, of which 998 were conducted in conjunction with a preapproval inspection. In contrast, FDA conducted 9,694 domestic establishment inspections that included a GMP component, of which 7,742 were not conducted in conjunction with a preapproval inspection. Figure 3 shows a comparison of foreign and domestic inspections, by type of inspection.

**Figure 3: Number of FDA Foreign and Domestic Establishment Inspections, by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007**




Source: GAO analysis of FDA data.

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA's funding for its domestic and foreign inspection programs is consistent with this approach. From fiscal year 2002 through fiscal year 2007, FDA dedicated more funding to domestic establishment inspections than foreign establishment inspections. The agency dedicated more funding to conduct foreign preapproval inspections than foreign GMP surveillance inspections, as shown in table 3.

**Table 3: FDA Funding for Foreign and Domestic Inspections Related to Human Drugs, Fiscal Year 2002 through Fiscal Year 2007**

| Activity (dollars in thousands) | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007[a] |
|---|---|---|---|---|---|---|
| **Foreign** | | | | | | |
| Preapproval inspections | $8,274 | $8,515 | $8,406 | $8,604 | $7,544 | $7,558 |
| Postapproval inspections | 5,256 | 5,177 | 5,150 | 5,224 | 5,261 | 5,191 |
| **Domestic** | | | | | | |
| Preapproval inspections | 21,846 | 23,008 | 23,965 | 25,213 | 21,775 | 23,532 |
| Postapproval inspections | 23,102 | 28,601 | 27,989 | 28,270 | 27,607 | 28,452 |

Source: GAO analysis of FDA data.

[a]Fiscal year 2007 funding is estimated.

## FDA's Risk-Based Process Is Used to Select Relatively Few Foreign Establishments for GMP Surveillance Inspections

Relatively few foreign establishments identified through CDER's risk-based site selection process are selected for GMP surveillance inspections. In fiscal year 2007, after using this process to rank the 3,249 establishments by their potential risk level, CDER forwarded to ORA a list of 104 foreign establishments that it considered to be a high priority for inspection. Of these, CDER requested that ORA complete GMP surveillance inspections of 25 establishments and FDA officials estimated that about 30 such inspections were actually completed in fiscal year 2007. In fiscal year 2008, CDER submitted a list of 110 foreign establishments to ORA, with a negotiated target of at least 50 inspections.

The application of the risk-based site selection process does not ensure that the foreign establishments posing the greatest potential risk are selected for GMP surveillance inspections. First, FDA officials acknowledge that they do not have an accurate list of foreign establishments manufacturing drugs for the U.S. market to use in the application of the risk-based process. Second, the usefulness of the risk-based process is weakened by the incomplete and possibly inaccurate information on those foreign establishments that FDA has not inspected recently, as well as those that have never been the subject of a GMP surveillance inspection. As a consequence, FDA lacks sufficient data to make an accurate assessment of the potential risk of such establishments. FDA recognized the effect of such data limitations on the domestic application of the risk-based process and undertook a data quality improvement initiative in fiscal year 2005, but it has yet to make a comparable effort to improve its data on foreign establishments.

To help account for the differences in information available to FDA between foreign establishments that have and have not been inspected, the agency categorizes establishments into one of three groups for the purposes of examining risk scores: (1) those that have received a GMP surveillance inspection since fiscal year 2000; (2) those that have not received a GMP surveillance inspection since fiscal year 2000, but have received another type of inspection in that time (for example, a preapproval inspection or a veterinary drugs inspection); and (3) those that may never have received an inspection.[25] These groups were created to account for limitations in the data and are not designed to indicate relative risk among groups. FDA officials told us that risk scores can be more readily compared within a group, than among groups. In 2007, FDA selected 33 establishments from the first group, 31 from the second group, and 40 from the third group to create the list of 104 establishments it submitted to ORA.

FDA officials indicated that they do not know if the establishments on the prioritized list forwarded to ORA differ significantly from each other in risk level. Consequently, they do not necessarily select the highest ranked establishments and therefore consider the locations of other planned inspections in making a final determination of foreign establishments from the prioritized list for GMP surveillance inspections. According to FDA officials, this gives them needed flexibility to make selections that will make efficient use of available resources. For example, if ORA is sending an investigator and laboratory analyst to a particular region in China for a preapproval inspection and an establishment in the same region appears on the prioritized list for GMP surveillance inspections, ORA might add this establishment to the inspection itinerary.

[25]This third group may include registered establishments whose drugs are imported into the United States. However, some establishments in this group may have received an inspection under a different FEI number, be shippers rather than manufacturers, only manufacture products other than human drugs, or never have or no longer have their drugs imported. FDA was unable to provide counts of how many establishments fall into each of these subcategories.

## Challenges Unique to Foreign Inspections Influence the Manner in Which FDA Conducts Such Inspections

Inspections of foreign drug establishments pose unique challenges to FDA—in both human resources and logistics. For example, unlike domestic inspections, FDA does not have a dedicated staff devoted to conducting foreign inspections and relies on volunteers. In addition, unlike domestic GMP surveillance inspections, foreign establishment GMP surveillance inspections are announced in advance and inspections cannot be easily extended due to travel itineraries that involve more than one establishment. Other factors, such as language barriers, can also add complexity to the challenge of completing foreign establishment inspections.

According to FDA officials, the agency does not have a dedicated staff to conduct foreign inspections. They explained that the same investigators and laboratory analysts are responsible for conducting both foreign and domestic inspections. These staff members must meet certain criteria in terms of their experience and training to conduct inspections of foreign establishments. For example, they are required to take certain training courses and have at least 3 years of experience conducting domestic inspections before they can be considered to conduct a foreign inspection. FDA reported that it currently has approximately 335 employees who are qualified to conduct foreign inspections of drug manufacturers. Approximately 250 of these employees are investigators and 85 are laboratory analysts. These counts do not represent the number of individuals that actually conduct foreign inspections in a given year. Not all investigators and laboratory analysts who are qualified to conduct a foreign inspection do so in a given year, while others may perform multiple inspections during the same period. Using data from FACTS, we found that the total number of employees conducting pre-approval and GMP surveillance inspections of drug manufacturing establishments, either foreign or domestic, decreased from 587 in fiscal year 2002 to 446 in fiscal year 2007, as shown in table 4. However, of these, the number of employees who conducted foreign inspections of drug manufacturers increased from 100 to 141 during that same period. While an investigator and analyst team may participate in foreign inspections, FDA officials stated that in certain circumstances, such as inspections that do not involve the review of laboratory facilities, only an investigator is sent.

**Table 4: Number of FDA Employees Conducting Inspections, Fiscal Year 2002 through Fiscal Year 2007**

| Location of inspection | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007[a] |
|---|---|---|---|---|---|---|
| Employees who conducted foreign inspections | 100 | 94 | 117 | 114 | 102 | 141 |
| Employees who conducted foreign or domestic inspections | 587 | 595 | 539 | 512 | 478 | 446 |

Source: GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA relies on investigators and laboratory analysts to volunteer to conduct foreign inspections. FDA officials told us that it is difficult to recruit investigators and laboratory analysts to voluntarily travel to certain countries. However, officials noted that the agency provides various incentives to recruit employees for foreign inspection assignments. For example, employees receive a $300 bonus for each three week trip completed. FDA indicated that if the agency could not find an individual to volunteer for a foreign inspection trip, it would mandate the travel. However, FDA does not typically send investigators and laboratory analysts to countries for which the U.S. Department of State has issued a travel warning nor would it mandate travel to such a country.[26] We found that 49 foreign establishments registered as manufacturers of drugs for the U.S. market were located in 10 countries that had travel warnings posted as of October 2007.[27] However, FDA officials told us that in the past they have conducted inspections in countries with travel warnings. They also provided us with one example in which an establishment in a country with a travel warning hired security through the U.S. Department of State to protect the inspection team.

FDA also faces several logistical challenges in conducting inspections of foreign drug manufacturing establishments. FDA guidance states that inspections at foreign facilities are to be approached in the same manner as domestic inspections. However, the guidance notes that one main difference posing a significant challenge to the inspection team abroad is the logistics borne by the program itself. For example, FDA is unable to conduct unannounced inspections of foreign drug manufacturers, as it sometimes does with domestic manufacturers. FDA policy states that the

[26]Travel warnings are issued when the U.S. Department of State recommends that Americans avoid travel to a certain country.

[27]These ten countries are Colombia, the Democratic Republic of the Congo, Haiti, Indonesia, Israel, Kenya, Nigeria, Pakistan, the Philippines, and Saudi Arabia.

agency, with few exceptions, initiates inspections of establishments without prior notification to the specific establishment or its management so that the inspection team can observe the establishment under conditions that represent normal day-to-day activities.[28] However, prior notification is routinely provided to foreign establishments. FDA recognizes that the time and expense associated with foreign travel requires them to ensure that the foreign establishment's managers are available and that the production line being inspected is operational during the inspection. In addition, FDA does not have explicit authority to inspect establishments in foreign countries, and it therefore may have to obtain permission from the government and company prior to the inspection. FDA officials explained that, in some cases, investigators and laboratory analysts may need to obtain a visa or letters of invitation to enter the country in which the establishment is located. In addition, FDA does not have the same flexibility to extend the length of foreign inspection trips if problems are encountered as it does with domestic inspections because of the need to maintain the inspection schedule, which FDA officials told us typically involves inspections of multiple establishments in the same country.

FDA officials also told us that language barriers can make foreign inspections more difficult to conduct than domestic inspections. The agency does not generally provide translators in foreign countries, nor does it require that foreign establishments provide independent interpreters. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, who may not be a translator by training, rather than rely on an independent translator.

## Concluding Observations

Millions of Americans depend on the safety and effectiveness of the drugs they take. More than nine years ago we reported that FDA needed to make improvements in its foreign drug inspection program. Yet, our preliminary work indicates that fundamental flaws that we identified in the management of this program in 1998, continue to persist. FDA still does not have a reliable list of foreign establishments that are subject to inspection. As more imported drugs enter the United States, it becomes increasingly important that foreign establishments receive appropriate

[28]ORA Field Management Directive No. 112A, Prior Notification to FDA Regulated Industries of Impending Inspections, August 1996. However, for both domestic and foreign preapproval inspections, FDA provides prior notification to the establishment.

scrutiny. We understand that FDA currently cannot inspect all foreign establishments every few years. We also recognize that FDA has taken steps to improve its management of the foreign drug inspection program by enhancing the risk-based process it uses to select establishments for GMP surveillance inspections. In addition, FDA is pursuing an initiative that is intended to improve its identification of foreign drug establishments. However, until FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized, and safe.

Mr. Chairman, this completes my prepared statement, I would be happy to respond to any questions you or the other Members of the subcommittee may have at this time.

## Contacts and Acknowledgments

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# MEDICAL DEVICES

# Challenges for FDA in Conducting Manufacturer Inspections

Statement of Marcia Crosse, Director
Health Care


GAO-08-428T

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# Highlights

Highlights of GAO-08-428T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

January 29, 2008

## MEDICAL DEVICES

## Challenges for FDA in Conducting Manufacturer Inspections

### Why GAO Did This Study

As part of the Food and Drug Administration's (FDA) oversight of the safety and effectiveness of medical devices marketed in the United States, it inspects domestic and foreign establishments where these devices are manufactured. To help FDA address shortcomings in its inspection program, the Medical Device User Fee and Modernization Act of 2002 required FDA to accredit third parties to inspect certain establishments. In response, FDA has implemented two such voluntary programs. GAO previously reported on the status of one of these programs, citing concerns regarding its implementation and factors that may influence manufacturers' participation. (Medical Devices: Status of FDA's Program for Inspections by Accredited Organizations, GAO-07-157, January 2007.)

This statement (1) assesses FDA's management of inspections of establishments—particularly those in foreign countries—manufacturing devices for the U.S. market, and (2) provides the status of FDA's programs for third-party inspections of medical device manufacturing establishments. GAO interviewed FDA officials; reviewed pertinent statutes, regulations, guidance, and reports; and analyzed information from FDA databases. GAO also updated its previous work on FDA's programs for inspections by accredited third parties.

To view the full product, including the scope and methodology, click on GAO-08-428T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

### What GAO Found

FDA has not met the statutory requirement to inspect certain domestic establishments manufacturing medical devices every 2 years, and the agency faces challenges inspecting foreign establishments. FDA primarily inspected establishments located in the United States. The agency has not met the biennial inspection requirement for domestic establishments manufacturing medical devices that FDA has classified as high risk, such as pacemakers, or medium risk, such as hearing aids. FDA officials estimated that the agency has inspected these establishments every 3 years (for high risk devices) or 5 years (for medium risk devices). There is no comparable requirement to inspect foreign establishments, and agency officials estimate that these establishments have been inspected every 6 years (for high risk devices) or 27 years (for medium risk devices). FDA faces challenges in managing its inspections of foreign medical device establishments. Two databases that provide FDA with information about foreign medical device establishments and the products they manufacture for the U.S. market contain inaccuracies that create disparate estimates of establishments subject to FDA inspection. Although comparing information from these two databases could help FDA determine the number of foreign establishments marketing medical devices in the United States, these databases cannot exchange information and any comparisons must be done manually. Finally, inspections of foreign medical device manufacturing establishments pose unique challenges to FDA in human resources and logistics.

Few inspections of medical device manufacturing establishments have been conducted through FDA's two accredited third-party inspection programs—the Accredited Persons Inspection Program and the Pilot Multi-purpose Audit Program (PMAP). From March 11, 2004—the date when FDA first cleared an accredited organization to conduct independent inspections—through January 11, 2008, five inspections have been conducted by accredited organizations through FDA's Accredited Persons Inspection Program. An incentive to participation in the program is the opportunity to reduce the number of inspections conducted to meet FDA and other countries' requirements. Disincentives include bearing the cost for the inspection, particularly when the consequences of an inspection that otherwise might not occur in the near future could involve regulatory action. The Food and Drug Administration Amendments Act of 2007 made several changes to program eligibility requirements that could result in increased participation by manufacturers. PMAP was established on September 7, 2006, and as of January 11, 2008, two inspections had been conducted by an accredited organization through this program, which is more limited than the Accredited Persons Inspection Program. The small number of inspections completed to date by accredited third-party organizations raises questions about the practicality and effectiveness of establishing similar programs that rely on third parties to quickly help FDA fulfill its responsibilities.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you examine how the Food and Drug Administration (FDA) has been meeting its regulatory responsibilities. One area of FDA responsibility is the regulation of medical devices[1]—such as hearing aids and pacemakers—marketed in the United States, whether manufactured in domestic or foreign establishments.[2] FDA classifies medical devices into one of three classes based on degree of potential risk and level of control needed to reasonably ensure safety and effectiveness.[3] Inspection of establishments is FDA's primary means of assuring that the safety and effectiveness of medical devices are not jeopardized by poor manufacturing practices. Requirements governing domestic and foreign inspections differ. Specifically, FDA is required to inspect domestic establishments that manufacture class II (medium risk) or III (high risk) medical devices every 2 years.[4] There is no comparable requirement to inspect foreign establishments.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) addressed concerns about FDA's ability to meet its responsibilities for inspecting medical device manufacturing establishments.[5] MDUFMA included provisions designed to (1) increase the number of inspected medical device manufacturing establishments and (2) help manufacturers

[1]Medical devices include instruments, apparatuses, machines, and implants that are intended for use to diagnose, cure, treat, or prevent disease, or to affect the structure or any function of the body. 21 U.S.C. § 321(h).

[2]FDA regulations define an establishment as a place of business under one management at one general physical location at which a device is manufactured, assembled, or otherwise processed. 21 C.F.R. § 807.3(c) (2007). Medical device manufacturers may have more than one establishment. We use the term "manufacture" to refer to activities including manufacturing, preparing, and processing devices.

[3]21 U.S.C. § 360c. Medical devices are classified into one of three classes. Class I includes "low risk" devices, such as tongue depressors, elastic bandages, and bedpans. Class II includes "medium risk" devices, such as syringes, hearing aids, and electrocardiograph machines. Class III includes "high risk" devices, such as heart valves, pacemakers, and defibrillators.

[4]21 U.S.C. § 360(h). There is no statutory requirement for inspection of class I medical device manufacturing establishments, and FDA does not routinely inspect them. However, FDA periodically inspects establishments manufacturing surgeon's gloves and patient examination gloves, which are both class I medical devices, due to ongoing problems with leakage. FDA also periodically inspects manufacturers of randomly selected class I devices.

[5]See Pub. L. No. 107-250, § 201, 116 Stat. 1588, 1602-09 (2002) (codified as amended at 21 U.S.C. § 374(g)).

meet the inspection requirements of both the United States and foreign countries in a single inspection. Specifically, MDUFMA required FDA to accredit third-party organizations to conduct inspections of certain domestic and foreign establishments.[6] In response, FDA implemented its Accredited Persons Inspection Program, which permits certain establishments to voluntarily request inspections from third-party organizations to meet inspectional requirements. In January 2007, we reported on the status of this program citing, among other things, concerns regarding its implementation and potential incentives and disincentives that may influence manufacturers' participation.[7] Additionally, in partnership with Health Canada,[8] FDA has established another program for inspection by accredited third parties—the Pilot Multi-purpose Audit Program (PMAP)—that allows accredited organizations to conduct a single inspection to meet the regulatory requirements of both countries. A report by the House of Representatives Committee on Energy and Commerce that accompanied MDUFMA stated that inspections by accredited third parties would permit FDA to focus the agency's inspection resources on manufacturers that have greater problems and devices that present higher risks.[9]

In addition to the questions about medical devices that led to the creation of FDA's third-party inspection program, questions have also been raised about how FDA is meeting its regulatory responsibilities in other program areas, such as drugs. In November 2007, we testified on our preliminary findings regarding FDA's program for inspecting foreign drug manufacturers.[10] Our findings suggested that FDA conducted infrequent inspections; had weaknesses in its data systems, including conflicting information on the number of foreign establishments; and faced challenges unique to foreign inspections, including those involving human resource issues. (See app. I for a summary of that testimony. We plan to

[6]In this report, unless otherwise noted, when we discuss inspections, we are referring to those conducted by FDA investigators.

[7]GAO, *Medical Devices: Status of FDA's Program for Inspections by Accredited Organizations*, GAO-07-157 (Washington, D.C.: Jan. 5, 2007).

[8]Health Canada is the governmental entity that regulates medical devices marketed in Canada.

[9]H.R. Rep. No. 107-728, pt. 1, at 35-36 (2002).

[10]GAO, *Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, GAO-08-224T (Washington, D.C.: Nov. 1, 2007).

issue a final report at a later date.) Also in November 2007, a subcommittee of the FDA Science Board[11] issued a report that identified growing demands on FDA, including the globalization of the industries that FDA regulates. The report found that disparities between FDA's responsibilities and its available resources—including human resources—have resulted in serious weaknesses that jeopardize the agency's ability to meet current and emerging regulatory responsibilities.[12] The subcommittee's report noted that these weaknesses include inadequate inspections of manufacturers. It also emphasized that FDA's information technology infrastructure is obsolete and unstable; provides an insufficient basis to access, integrate, and analyze data; and is subject to frequent system failures.

Third-party organizations have been identified as one mechanism that could help FDA address shortcomings in inspection programs, beyond the programs for medical devices. The federal Interagency Working Group on Import Safety recently suggested that the use of third-party organizations could provide FDA with information to help the agency target its inspection resources to those products of greatest risk.[13] In addition, we recommended that FDA consider developing a third-party inspection program to help it meet its responsibilities for inspecting foreign firms importing seafood to the United States.[14]

Given the recent questions regarding FDA's inspection programs and suggestions that third-party organizations could supplement FDA's resources, you asked for information on FDA's management of its medical device inspection program. My remarks will focus on (1) our assessment of FDA's program for inspecting establishments that manufacture medical

[11]The Science Board, which is an advisory board to the commissioner of FDA, provides advice on, among other things, specific complex and technical issues as well as emerging issues within the scientific community.

[12]FDA Science Board, Subcommittee on Science and Technology, *FDA Science and Mission at Risk* (November 2007), http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_00_index.html (accessed Jan. 18, 2008).

[13]In July 2007, the Interagency Working Group on Import Safety was established to conduct a comprehensive review of current import safety practices and determine where improvements could be made. Interagency Working Group on Import Safety, *Action Plan for Import Safety: A roadmap for continual improvement* (November 2007), http://www.importsafety.gov/report/actionplan.pdf (accessed Dec. 6, 2007).

[14]See GAO, *Food Safety: FDA's Imported Seafood Safety Program Shows Some Progress, but Further Improvements are Needed*, GAO-04-246 (Washington, D.C.: Jan. 30, 2004).

devices for the U.S. market, particularly those located in foreign countries and (2) the status of FDA's programs for third-party inspections of medical device manufacturing establishments. Today, in a separate statement, we are also discussing the federal oversight of food safety as a high-risk area and ways in which FDA can better leverage its resources.[15] These and other recent testimonies on drug safety and food safety offer some observations on FDA's inspection program capacity.

To address these issues, we interviewed officials from FDA's Center for Devices and Radiological Health (CDRH) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the medical device inspection program.[16] We reviewed pertinent statutes and regulations, as well as agency documents that provide guidance on FDA's inspection requirements and programs for inspections by accredited third parties. To assess FDA's program for inspecting establishments that manufacture medical devices, we obtained information from FDA's Device Registration and Listing System (DRLS), as of September 19, 2007; Field Accomplishments and Compliance Tracking System (FACTS) for fiscal year 2002 through fiscal year 2007; and Operational and Administrative System for Import Support (OASIS) for fiscal year 2007. We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them, (2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of data elements from DRLS and FACTS. We found the data in the FACTS database sufficiently reliable for our purposes. We also found that DRLS was sufficiently reliable, to the extent that it accurately reflects information provided by domestic and foreign establishments that register to market medical devices in the United States. However, we determined that these data do not necessarily reflect the number of establishments that manufacture medical devices for the U.S. market. In addition, we found that OASIS is likely to overestimate the number of foreign establishments whose medical devices have been imported into the United States, due to uncorrected errors in the data. Therefore, we present

[15]GAO, *Federal Oversight of Food Safety: FDA's Food Protection Plan Proposes Positive First Steps, but Capacity to Carry Them Out is Critical*, GAO-08-435T (Washington, D.C.: Jan. 29, 2008).

[16]Within FDA, the Center for Biologics Evaluation and Research regulates medical devices involved in human immunodeficiency virus (HIV) testing and the collection, processing, testing, manufacture, and administration of licensed blood, blood components, and cellular products. We did not include medical devices regulated by this center in the scope of our work.

information from both DRLS and OASIS to illustrate the variability in information that FDA's databases provide to agency officials on this topic. These data represent the best information available and are what FDA relies on to manage its domestic and foreign medical device inspection activities.

To examine the status of FDA's programs for third-party inspections, we received FDA data on the number of inspections conducted by accredited third parties from March 11, 2004—the date when FDA first cleared an accredited organization to conduct inspections—through January 11, 2008. This updates the data we obtained for our January 2007 report for which data collection ended on October 31, 2006. We also obtained information from FDA about other critical aspects of their programs for inspections by accredited third parties, such as the number of accredited organizations. To gain perspective on recent changes to FDA's programs for inspections by accredited third parties, we contacted representatives of the same 13 affected entities we interviewed for our January 2007 report on this topic.[17] We received responses from 2 of 4 accredited organizations, 2 of 3 organizations that represent medical device manufacturers, and 1 of 6 manufacturers. We received technical comments on a draft of this statement from FDA, which we incorporated, as appropriate. We conducted this performance audit from December 2007 to January 2008, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

In summary, we found that FDA has not met the requirement to inspect domestic establishments manufacturing class II or III medical devices every 2 years and faces challenges in inspecting foreign establishments. FDA primarily inspected domestic establishments. FDA officials estimated that the agency has inspected domestic class II manufacturers every 5 years and domestic class III manufacturers every 3 years. There is no comparable requirement to conduct foreign inspections and FDA has conducted relatively few. Officials estimated the agency has inspected foreign class II manufacturers every 27 years and foreign class III

[17]These affected entities included accredited organizations, organizations that represent medical device manufacturers, and medical device manufacturers.

manufacturers every 6 years. In addition, FDA faces challenges in managing its foreign medical device inspection program. Two databases that provide FDA with information about foreign medical device establishments and the products they manufacture for the U.S. market contain inaccuracies that create divergent estimates of establishments subject to FDA inspection. Despite the divergent estimates, FDA does not routinely verify these data. Although comparing information from these two databases could help FDA determine the number of foreign establishments marketing medical devices in the United States, these databases cannot exchange information and any comparisons must be done manually. While the agency has taken steps to improve these databases, it is too soon to know if these changes will improve FDA's data. Finally, inspections of foreign medical device manufacturing establishments pose unique challenges to FDA, such as difficulties in recruiting investigators to voluntarily travel to certain countries and in extending trips if problems are identified during inspections. Our results are consistent with our November 2007 testimony on FDA's foreign drug inspection program, as well as the findings of the FDA Science Board.

Few inspections of medical device manufacturing establishments have been conducted through FDA's two programs for inspections by accredited third parties—the Accredited Persons Inspection Program and PMAP. From March 11, 2004—the date when FDA first cleared an accredited organization to conduct inspections—through January 11, 2008, five inspections have been conducted by accredited organizations through FDA's Accredited Persons Inspection Program. Manufacturers' decisions to request an inspection by an accredited organization might be influenced by both potential incentives and disincentives. An incentive to participation in the program is the opportunity to reduce the number of inspections conducted to meet FDA and other countries' requirements. Disincentives include bearing the cost for the inspection, particularly when the consequences of an inspection that otherwise may not occur in the near future could involve regulatory action. The Food and Drug Administration Amendments Act of 2007 (FDAAA) changed the requirements for inspections by accredited third parties in several ways, which could result in increased participation by manufacturers, although it is too soon to tell. For example, an eligibility requirement that foreign establishments be periodically inspected by FDA was eliminated. Device manufacturers may also request an inspection by an accredited third party through PMAP, which was established on September 7, 2006. As of January 11, 2008, two inspections had been conducted by an accredited organization through PMAP, which is more limited than the Accredited Persons Inspection Program. The small number of inspections completed

to date by accredited third-party organizations raises questions about the practicality and effectiveness of establishing similar programs that rely on third parties to help FDA fulfill other responsibilities.

## Background

FDA is responsible for overseeing the safety and effectiveness of medical devices that are marketed in the United States, whether manufactured in domestic or foreign establishments. All establishments that manufacture medical devices for marketing in the United States must register with FDA.[18] As part of its efforts to ensure the safety, effectiveness, and quality of medical devices, FDA is responsible for inspecting certain domestic and foreign establishments to ensure that they meet manufacturing standards established in FDA's quality system regulation.[19] FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to prevent the importation of products manufactured at establishments that refuse to allow an FDA inspection.[20] Unlike food, for which FDA primarily relies on inspections at the border, physical inspection of manufacturing establishments is a critical mechanism in FDA's process to ensure that medical devices and drugs are safe and effective and that manufacturers adhere to good manufacturing practices.

Within FDA, CDRH assures the safety and effectiveness of medical devices. Among other things, CDRH works with ORA, which conducts inspections of both domestic and foreign establishments to ensure that devices are produced in conformance with federal statutes and regulations, including the quality system regulation. FDA may conduct inspections before and after medical devices are approved or otherwise cleared to be marketed in the United States.

- Premarket inspections are conducted before FDA will approve U.S. marketing of a new medical device that is not substantially equivalent to

[18]21 U.S.C. § 360(b), (i).

[19]21 C.F.R. pt. 820 (2007). The quality system regulation requires, among other things, that domestic or foreign manufacturers have a quality system in place to implement current good manufacturing practices in the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for human use in the United States. A quality system includes the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

[20]See 21 U.S.C. § 381(a); 21 C.F.R. § 820.1(d) (2007).

one that is already on the market.[21] Premarket inspections primarily assess manufacturing facilities, methods, and controls and may verify pertinent records.

- Postmarket inspections are conducted after a medical device has been approved or otherwise cleared to be marketed in the United States and include several types of inspections: (1) Quality system inspections are conducted to assess compliance with applicable FDA regulations, including the quality system regulation to ensure good manufacturing practices and the regulation requiring reporting of adverse events.[22] These inspections may be comprehensive or abbreviated, which differ in the scope of inspectional activity. Comprehensive postmarket inspections assess multiple aspects of the manufacturer's quality system, including management controls, design controls, corrective and preventative actions, and production and process controls. Abbreviated postmarket inspections assess only some of these aspects, but always assess corrective and preventative actions. (2) For-cause and compliance follow-up inspections are initiated in response to specific information that raises questions or problems associated with a particular establishment. (3) Postmarket audit inspections are conducted within 8 to 12 months of a premarket application's approval to examine any changes in the design, manufacturing process, or quality assurance systems.

  FDA determines which establishments to inspect using a risk-based strategy. High priority inspections include premarket approval inspections for class III devices, for-cause inspections, inspections of establishments that have had a high frequency of device recalls, and other devices and manufacturers FDA considers high risk. The establishment's inspection history may also be considered. A provision in FDAAA may assist FDA in making decisions about which establishments to inspect because it authorizes the agency to accept voluntary submissions of audit reports addressing manufacturers' conformance with internationally established standards for the purpose of setting risk-based inspectional priorities.[23]

[21]Currently, most medical devices are cleared for marketing in the United States because they are "substantially equivalent" to a marketed device. FDA generally does not conduct premarket inspections of establishments manufacturing these types of medical devices.

[22]21 C.F.R. pt. 803 (2007).

[23]Pub. L. No. 110-85, § 228, 121 Stat. 858 (2007).

FDA's programs for domestic and foreign inspections by accredited third parties provide an alternative to the traditional FDA-conducted comprehensive postmarket quality system inspection for eligible manufacturers of class II and III medical devices. MDUFMA required FDA to accredit third persons—which are organizations—to conduct inspections of certain establishments. In describing this requirement, the House of Representatives Committee on Energy and Commerce noted that some manufacturers have faced an increase in the number of inspections required by foreign countries, and that the number of inspections could be reduced if the manufacturers could contract with a third-party organization to conduct a single inspection that would satisfy the requirements of both FDA and foreign countries.[24] Manufacturers that meet eligibility requirements may request a postmarket inspection by an FDA-accredited organization.[25] The eligibility criteria for requesting an inspection of an establishment by an accredited organization include that the manufacturer markets (or intends to market) a medical device in a foreign country and the establishment to be inspected must not have received warnings for significant deviations from compliance requirements on its last inspection.[26]

MDUFMA also established minimum requirements for organizations to be accredited to conduct third-party inspections, including protecting against financial conflicts of interest and ensuring the competence of the organization to conduct inspections. FDA developed a training program for inspectors from accredited organizations that involves both formal classroom training and completion of three joint training inspections with FDA. Each individual inspector from an accredited organization must

[24]H.R. Rep. No. 107-728, pt. 1, at 32-36 (2002). Some foreign countries have accredited, certified, or otherwise recognized organizations to conduct inspections. We use the term "single inspection" to mean a complete inspection that covers all requirements of two or more countries, without repeating those activities covered under more than one set of requirements. A complete inspection can be conducted during a single block of time or in multiple phases. Two or more separate inspection reports could be generated on the basis of that single inspection.

[25]Accredited organizations may conduct comprehensive postmarket quality system inspections, but not other types of inspections of establishments that FDA has the authority to conduct, such as premarket or for-cause inspections. FDA may conduct its own inspections of establishments even after inspection by an accredited organization.

[26]21 U.S.C. § 374(g). FDAAA eliminated certain previously established eligibility requirements. For example, it eliminated a limitation on the number of consecutive inspections allowed by an accredited organization and a limitation that foreign establishments must be inspected periodically by FDA.

complete all training requirements successfully before being cleared to conduct independent inspections. FDA relies on manufacturers to volunteer to host these joint inspections, which count as FDA postmarket quality system inspections.

A manufacturer that is cleared to have an inspection by an accredited third party enters an agreement with the approved accredited organization and schedules an inspection. Once the accredited organization completes its inspection, it prepares a report and submits it to FDA, which makes the final assessment of compliance with applicable requirements. FDAAA added a requirement that accredited organizations notify FDA of any withdrawal, suspension, restriction, or expiration of certificate of conformance with quality systems standards (such as those established by the International Organization for Standardization) for establishments they inspected for FDA.[27]

In addition to the Accredited Persons Inspection Program, FDA has a second program for accredited third-party inspections of medical device establishments. On September 7, 2006, FDA and Health Canada announced the establishment of PMAP. This pilot program was designed to allow qualified third-party organizations to perform a single inspection that would meet the regulatory requirements of both the United States and Canada. The third-party organizations eligible to conduct inspections through PMAP are those that FDA accredited for its Accredited Persons Inspection Program (and that completed all required training for that program) and that are also authorized to conduct inspections of medical device establishments for Health Canada. To be eligible to have a third-party inspection through PMAP, manufacturers must meet all criteria established for the Accredited Persons Inspection Program. As with the Accredited Persons Inspection Program, manufacturers must apply to participate and be willing to pay an accredited organization to conduct the inspection.

FDA relies on multiple databases to manage its program for inspecting medical device manufacturing establishments.

- DRLS contains information on domestic and foreign medical device establishments that have registered with FDA. Establishments that are involved in the manufacture of medical devices intended for commercial

[27]21 U.S.C. § 374(g)(3)(F).

distribution in the United States are required to register annually with FDA. These establishments provide information to FDA, such as establishment name and address and the medical devices they manufacture. As of October 1, 2007, establishments are required to register electronically through FDA's Unified Registration and Listing System and certain medical device establishments pay an annual establishment registration fee, which in fiscal year 2008 is $1,706.[28]

- OASIS contains information on medical devices and other FDA-regulated products imported into the United States, including information on the establishment that manufactured the medical device. The information in OASIS is automatically generated from data managed by U.S. Customs and Border Protection, which are originally entered by customs brokers based on the information available from the importer.[29]

- FACTS contains information on FDA's inspections, including those of domestic and foreign medical device establishments. FDA investigators enter information into FACTS following completion of an inspection.

According to FDA data, more than 23,600 establishments that manufacture medical devices were registered as of September 2007, of which 10,600 reported that they manufacture class II or III medical devices.[30] More than half—about 5,600—of these establishments were located in the United States. As of September 2007, there were more registered establishments in China and Germany reporting that they manufacture class II or III medical devices than in any other foreign countries.[31] Canada, Taiwan, and the United Kingdom also had a large number of registered establishments. (See fig. 1.) Registered foreign establishments reported that they manufacture a variety of class II and III medical devices for the U.S.

[28]21 U.S.C. § 379j(a)(3), (b).

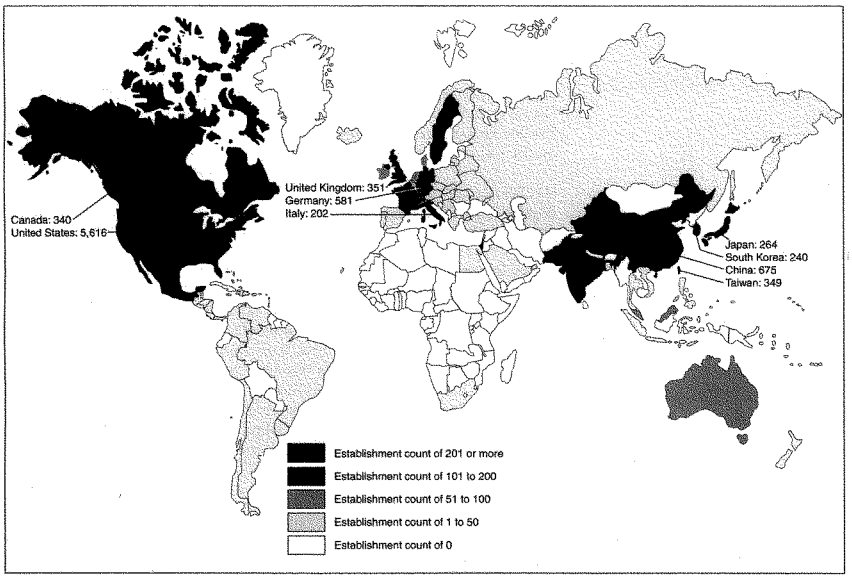
[29]Customs brokers are private individuals, partnerships, associations, or corporations licensed, regulated, and empowered by U.S. Customs and Border Protection to assist in meeting federal requirements governing imports and exports.

[30]Throughout this testimony, we use DRLS data because FDA officials told us that the agency would continue to use those data, as available on September 19, 2007, until it is confident that all device establishments required to register have done so through the new electronic system, FDA's Unified Registration and Listing System.

[31]Counts of registered establishments in China do not include establishments registered in Hong Kong or Taiwan as these establishments are tracked separately in DRLS.

market. For example, common class III medical devices included coronary stents,[32] pacemakers, and contact lenses.

**Figure 1: Registered Establishments That Reported Manufacturing Class II or Class III Medical Devices for the U.S. Market, by Country, September 2007**




Source: GAO analysis of FDA data.

Note: Counts of registered establishments in China do not include establishments registered in Hong Kong or Taiwan as these establishments are tracked separately in DRLS. In addition, DRLS contained one additional registered establishment for which location information was not available.

[32]A coronary stent is a small tube that is placed within a coronary artery to keep the vessel open.

## FDA Is Not Inspecting Domestic Establishments Biennially as Required and Faces Challenges in Inspecting Foreign Establishments

FDA has not met the statutory requirement to inspect domestic establishments manufacturing class II or III medical devices every 2 years. The agency conducted relatively few inspections of foreign establishments. The databases that provide FDA with data about the number of foreign establishments manufacturing medical devices for the U.S. market contain inaccuracies. In addition, inspections of foreign medical device manufacturing establishments pose unique challenges to FDA—both in human resources and logistics.

### FDA Is Not Inspecting Domestic Establishments Biennially and Inspects Relatively Few Foreign Establishments

From fiscal year 2002 through fiscal year 2007, FDA primarily inspected establishments located in the United States, where more than half of the 10,600 registered establishments that reported manufacturing class II or III medical devices are located. In contrast, FDA inspected relatively few foreign medical device establishments. During this period, FDA conducted an average of 1,494 domestic and 247 foreign establishment inspections each year.[33] This suggests that each year FDA inspects about 27 percent of registered domestic establishments that reported manufacturing class II or class III medical devices and about 5 percent of such foreign establishments. The inspected establishments were in the United States and 44 foreign countries. Of the foreign inspections, more than two-thirds were in 10 countries. Most of the countries with the highest number of inspections were also among those with the largest number of registered establishments that reported manufacturing class II or III medical devices. The lowest rate of inspections in these 10 countries was in China, where 64 inspections were conducted in this 6-year period and almost 700 establishments were registered. (See table 1.)

[33]We were unable to differentiate inspections according to medical device classification. FDA's inspection database contains the most recent information available to FDA about the class of device manufactured at the establishment, and consequently does not contain readily available information about the class of devices manufactured at the time of a specific inspection. As a result, the data we present include all inspections, regardless of the classification of the manufactured device or devices. According to FDA officials, FDA primarily conducts inspections of establishments manufacturing class II or III medical devices.

**Table 1: Number of FDA Inspections of Medical Device Establishments, Fiscal Year 2002 through Fiscal Year 2007**

| | Number of inspections[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Country | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007 | Total | Number of registered class II or III manufacturing establishments[b] |
| United States | 1,261 | 1,736 | 1,631 | 1,471 | 1,501 | 1,362 | **8,962**[c] | 5,616 |
| Germany | 39 | 30 | 34 | 51 | 25 | 52 | **231** | 581 |
| United Kingdom | 25 | 31 | 28 | 14 | 25 | 43 | **166** | 351 |
| Canada | 17 | 17 | 24 | 11 | 13 | 26 | **108** | 340 |
| Japan | 7 | 8 | 20 | 21 | 16 | 25 | **97** | 264 |
| Ireland | 15 | 22 | 13 | 13 | 16 | 11 | **90** | 67 |
| France | 16 | 14 | 17 | 14 | 12 | 10 | **83** | 190 |
| Switzerland | 6 | 12 | 19 | 9 | 7 | 18 | **71** | 134 |
| China[d] | 0 | 0 | 21 | 19 | 11 | 13 | **64** | 675[e] |
| Mexico | 10 | 7 | 12 | 8 | 12 | 11 | **60** | 143 |
| Italy | 8 | 7 | 10 | 6 | 13 | 11 | **55** | 202 |
| All other countries | 66 | 83 | 102 | 67 | 69 | 69 | **456** | 2,036 |
| ***Total*** | **1,470** | **1,967** | **1,931** | **1,704** | **1,720** | **1,651** | **10,443** | **10,600**[f] |

Source: GAO analysis of FDA data.

[a]We were unable to differentiate inspections according to medical device classification. FDA's inspection database contains the most recent information available to FDA about the class of device manufactured at the establishment, and consequently does not contain readily available information about the class of devices manufactured at the time of a specific inspection. As a result, the data we present include all inspections, regardless of the classification of the manufactured device or devices. According to FDA officials, FDA primarily conducts inspections of establishments manufacturing class II or III medical devices.

[b]These counts represent the number of registered establishments as of September 2007.

[c]In addition to inspections conducted by FDA personnel, from fiscal year 2002 through fiscal year 2007, FDA contracted with states to conduct 164 quality system inspections. These inspections are not included in the total.

[d]The inspection counts for China do not include inspections conducted in Hong Kong or Taiwan as these inspections are tracked separately in FACTS.

[e]Counts of registered establishments in China do not include establishments registered in Hong Kong or Taiwan as these establishments are tracked separately in DRLS.

[f]Registration numbers do not add to total because DRLS contained one additional registered establishment for which location information was not available.

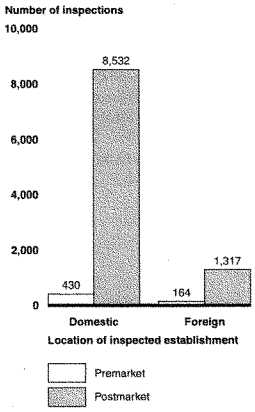
Despite its focus on domestic inspections, FDA has not met the statutory requirement to inspect domestic establishments manufacturing class II or III medical devices every 2 years. For domestic establishments, FDA officials estimated that, on average, the agency inspects class II

manufacturers every 5 years and class III manufacturers every 3 years. For foreign establishments—for which there is no comparable inspection requirement—FDA officials estimated that the agency inspects class II manufacturers every 27 years and class III manufacturers every 6 years.

FDA's inspections of medical device establishments, both domestic and foreign, are primarily postmarket inspections. While premarket inspections are generally FDA's highest priority, relatively few have to be performed in any given year.[34] Therefore, FDA focuses its resources on postmarket inspections. From fiscal year 2002 through fiscal year 2007, 95 percent of the 8,962 domestic establishment inspections and 89 percent of the 1,481 foreign establishment inspections were for postmarket purposes. (See fig. 2.)

[34]Currently, most medical devices are cleared for marketing in the United States because they are "substantially equivalent" to a marketed device. FDA generally does not conduct premarket inspections of establishments manufacturing these types of medical devices.

**Figure 2: Number of Inspections of Domestic and Foreign Establishments That Manufacture Medical Devices for the U.S. Market, by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007**




Source: GAO analysis of FDA data.

Note: If an inspection had both premarket and postmarket components, we classified it as a premarket inspection. Of the 430 domestic premarket inspections, 256 contained both premarket and postmarket components. Of the 164 foreign premarket inspections, 95 contained both premarket and postmarket components. FDA may conduct other types of inspections—such as a postmarket quality system, compliance follow-up, for-cause, or postmarket audit inspection—at the same establishment at which they are conducting a premarket inspection. These inspections may focus on different products manufactured at the same establishment.

## FDA's Databases Provide Inconsistent Information Regarding the Number of Foreign Medical Device Manufacturing Establishments Subject to Inspection

FDA's databases on registration and imported products provide divergent estimates regarding the number of foreign medical device manufacturing establishments. DRLS provides FDA with information about domestic and foreign medical device establishments and the products they manufacture for the U.S. market. According to DRLS, as of September 2007, 5,616 domestic and 4,983 foreign establishments that reported manufacturing a class II or III medical device for the U.S. market had registered with FDA.[35] However, these data contain inaccuracies because establishments may register with FDA but not actually manufacture a medical device or may manufacture a medical device that is not marketed in the United States. FDA officials told us that their more frequent inspections of domestic establishments allow them to more easily update information about whether a domestic establishment is subject to inspection.

In addition to DRLS, FDA obtains information on foreign establishments from OASIS, which tracks the import of medical devices. While not intended to provide a count of establishments, OASIS does contain information about the medical devices actually being imported into the United States and the establishments manufacturing them. However, inaccuracies in OASIS prevent FDA from using it to develop a list of establishments subject to inspection. OASIS contains duplicate records for a single establishment because of inaccurate data entry by customs brokers at the border. According to OASIS, in fiscal year 2007, there were as many as 22,008 foreign establishments that manufactured class II medical devices for the U.S. market and 3,575 foreign establishments that manufactured class III medical devices for the U.S. market.[36] Despite the divergent estimates of foreign establishments generated by DRLS and OASIS, FDA does not routinely verify the data within each database. Although comparing information from these two databases could help FDA determine the number of foreign establishments marketing medical devices in the United States, the databases cannot exchange information to be compared electronically and any comparisons are done manually.

Efforts are underway that could improve FDA's databases. FDA officials suggested that, because manufacturers are now required to pay an annual establishment registration fee, manufacturers may be more concerned

[35]DRLS contained one additional registered establishment for which location information was not available.

[36]According to FDA officials, a single establishment could be manufacturing more than one class of device.

about the accuracy of the registration data they submit. They also told us that, because of the registration fee, manufacturers may be less likely to register if they do not actually manufacture a medical device for the U.S. market. In addition, FDA officials stated that the agency is pursuing various initiatives to try to address the inaccuracies in OASIS, such as providing a unique identifier for each foreign establishment to reduce duplicate entries for individual establishments.

## Challenges Unique to Foreign Inspections Influence the Manner in Which FDA Conducts Such Inspections

Inspections of foreign establishments pose unique challenges to FDA—both in human resources and logistics. FDA does not have a dedicated cadre of investigators that only conduct foreign medical device establishment inspections; those staff who inspect foreign establishments also inspect domestic establishments. Among those qualified to inspect foreign establishments,[37] FDA relies on staff to volunteer to conduct inspections. FDA officials told us that it is difficult to recruit investigators to voluntarily travel to certain countries. However, they added that if the agency could not find an individual to volunteer for a foreign inspection trip, it would mandate the travel. Logistically, foreign medical device establishment inspections are difficult to extend even if problems are identified because the trips are scheduled in advance.[38] Foreign medical device establishment inspections are also logistically challenging because investigators do not receive independent translational support from FDA or the State Department and may rely on English-speaking employees of the inspected establishment or the establishment's U.S. agent to translate during an inspection.

[37]Staff members must meet certain criteria in terms of their experience and training to conduct inspections of foreign establishments. For example, they are required to take certain training courses and have at least 3 years of experience conducting domestic inspections before they can be considered qualified to conduct a foreign inspection.

[38]Typically, FDA investigators travel abroad for about 3 weeks at a time, during which they inspect approximately three establishments.

## Few Third-Party Inspections Are Conducted, but Recent Changes Could Eliminate Some Obstacles to Manufacturers' Participation

Few inspections of medical device manufacturing establishments have been conducted through FDA's two accredited third-party inspection programs—the Accredited Persons Inspection Program and PMAP. FDAAA specified several changes to the requirements for inspections by accredited third parties that could result in increased participation by manufacturers.

Few inspections have been conducted through FDA's Accredited Persons Inspection Program since March 11, 2004—the date when FDA first cleared an accredited organization to conduct independent inspections. Through January 11, 2008, five inspections had been conducted independently by accredited organizations (two inspections of domestic establishments and three inspections of foreign establishments), an increase of three since we reported on this program one year ago.[39]

As of January 11, 2008, 16 third-party organizations were accredited,[40] and individuals from 8 of these organizations had completed FDA's training requirements and been cleared to conduct independent inspections.[41] As of January 8, 2008, FDA and accredited organizations had conducted 44 joint training inspections.[42] Fewer manufacturers volunteered to host training inspections than have been needed for all of the accredited organizations

[39]In January 2007, we reported that two inspections had been independently conducted by accredited organizations through the Accredited Persons Inspection Program—one inspection of a domestic establishment and one inspection of a foreign establishment. GAO-07-157, 11.

[40]FDA officials told us that no additional organizations have applied for accreditation since we issued our January 2007 report.

[41]In January 2007, we reported that 7 of the 16 accredited organizations had been cleared to conduct independent inspections. GAO-07-157, 11. One additional accredited organization was cleared to conduct independent inspections on October 18, 2007. Specific foreign jurisdictions that have certified, accredited, or otherwise recognized one or more of the FDA-accredited organizations that have been cleared to conduct independent inspections include all member states of the European Community, Australia, Canada, New Zealand, Norway, Taiwan, and the United Kingdom. Of the 8 third-party organizations that have been cleared to conduct independent inspections through the Accredited Persons Inspection Program, 4 may conduct inspections through PMAP.

[42]In January 2007, we reported that FDA and accredited organizations had conducted 37 joint training inspections. GAO-07-157, 11.

to complete their training.[43] Moreover, scheduling these joint training inspections has been difficult. FDA officials told us that, when appropriate, staff are instructed to ask manufacturers to host a joint training inspection at the time they notify the manufacturers of a pending inspection. FDA schedules inspections a relatively short time prior to an actual inspection,[44] and as we reported in January 2007, some accredited organizations have not been able to participate because they had prior commitments.

As we reported in January 2007, manufacturers' decisions to request an inspection by an accredited organization might be influenced by both potential incentives and disincentives. According to FDA officials and representatives of affected entities, potential incentives to participation include the opportunity to reduce the number of inspections conducted to meet FDA and other countries' requirements. For example, one inspection conducted by an accredited organization was a single inspection designed to meet the requirements of FDA, the European Union, and Canada. Another potential incentive mentioned by FDA officials and representatives of affected entities is the opportunity to control the scheduling of the inspection by an accredited organization by working with the accredited organization. FDA officials and representatives of affected entities also mentioned potential disincentives to having an inspection by an accredited organization. These potential disincentives include bearing the cost for the inspection,[45] doubts about whether accredited organizations can cover multiple requirements in a single

[43]As we reported in January 2007, some representatives of affected entities speculated that manufacturers might not have volunteered to host training inspections because they believed that training inspections would require more time and effort for their staff (and would thus be more disruptive) than inspections conducted by fully trained personnel, or that manufacturers might have believed that training inspections would be more rigorous than nontraining inspections if the trainees and FDA personnel were to take particular care to demonstrate their thoroughness to each other.

[44]FDA generally notifies manufacturers about a week in advance of postmarket quality system inspections of domestic establishments and about 6 to 8 weeks in advance of postmarket quality system inspections of foreign establishments.

[45]In January 2007, we reported that representatives of accredited organizations indicated that the cost to manufacturers would vary depending on such factors as the size of the manufacturer and how much extra time would be required to assess compliance with FDA requirements. Representatives suggested that covering FDA's requirements could take 2 or more days in addition to the time spent assessing other countries' requirements, plus time for advance preparation and writing the inspection report. They speculated that they would probably charge manufacturers from $1,700 to $2,500 per day, plus the cost of travel and living expenses.

inspection, and uncertainty about the potential consequences of an inspection that otherwise may not occur in the near future—consequences that could involve regulatory action.

Changes specified by FDAAA have the potential to eliminate certain obstacles to manufacturers' participation in FDA's programs for inspections by accredited third parties that were associated with manufacturers' eligibility. For example, an eligibility requirement that foreign establishments be periodically inspected by FDA was eliminated. Representatives of the two organizations that represent medical device manufacturers with whom we spoke about FDAAA told us that the changes in eligibility requirements could eliminate certain obstacles and therefore potentially increase their participation. These representatives also noted that key incentives and disincentives to manufacturers' participation remain. FDA officials told us that they are currently revising their guidance to industry in light of FDAAA and expect to issue the revised guidance during fiscal year 2008. It is too soon to tell what impact these changes will have on manufacturers' participation.

FDA officials acknowledged that manufacturers' participation in the Accredited Persons Inspection Program has been limited. In December 2007, FDA established a working group to assess the successes and failures of this program and to identify ways to increase participation. Representatives of the two organizations that represent medical device manufacturers with whom we recently spoke stated that they believe manufacturers remain interested in the Accredited Persons Inspection Program. The representative of one large, global manufacturer of medical devices told us that it is in the process of arranging to have 20 of its domestic and foreign device manufacturing establishments inspected by accredited third parties.

As of January 11, 2008, two inspections, both of domestic establishments, had been conducted through PMAP, FDA's second program for inspections by accredited third parties. Although it is too soon to tell what the benefits of PMAP will be, the program is more limited than the Accredited Persons Inspection Program and may pose additional disincentives to participation by both manufacturers and accredited organizations. Specifically, inspections through PMAP would be designed to meet the requirements of the United States and Canada, whereas inspections conducted through the Accredited Persons Inspection Program could be designed to meet the requirements of other countries. In addition, two of the five representatives of affected entities noted that in contrast to inspections conducted through the Accredited Persons

Inspection Program, inspections conducted through PMAP could undergo additional review by Health Canada. Health Canada will review inspection reports submitted through this pilot program to ensure they meet its standards. This extra review poses a greater risk of unexpected outcomes for the manufacturer and the accredited organization, which could be a disincentive to participation in PMAP that is not present with the Accredited Persons Inspection Program.

## Concluding Observations

Americans depend on FDA to ensure the safety and effectiveness of medical products, including medical devices, manufactured throughout the world. However, our findings regarding inspections of medical device manufacturers indicate weaknesses that mirror those presented in our November 2007 testimony regarding inspections of foreign drug manufacturers. In addition, they are consistent with the FDA Science Board's findings that FDA's ability to fulfill its regulatory responsibilities is jeopardized, in part, by information technology and human resources challenges. We recognize that FDA has expressed the intention to improve its data management, but it is too early to tell whether the intended changes will ultimately enhance the agency's ability to manage its inspection programs. We and others have suggested that the use of accredited third parties could improve FDA's ability to meet its inspection responsibilities. However, the implementation of its programs for inspecting medical device manufacturers has resulted in little progress. To date, its programs for inspections by accredited third parties have not assisted FDA in meeting its regulatory responsibilities nor have they provided a rapid or substantial increase in the number of inspections performed by these organizations, as originally intended. Although recent statutory changes to the requirements for inspections by accredited third parties may encourage greater participation in these programs, the lack of meaningful progress raises questions about the practicality and effectiveness of establishing similar programs that rely on third parties to quickly help FDA fulfill other responsibilities.

Mr. Chairman, this completes my prepared statement, I would be happy to respond to any questions you or the other Members of the subcommittee may have at this time.

## Contacts and Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may found on the last page of this testimony. Geraldine Redican-Bigott, Assistant Director; Kristen Joan Anderson; Katherine Clark; Robert Copeland; William Hadley; Cathy Hamann; Mollie Hertel; Julian Klazkin; Lisa Motley; Daniel Ries; and Suzanne Worth made key contributions to this testimony.

# Appendix I: Summary of GAO Testimony on FDA's Program for Inspecting Foreign Drug Manufacturers

In congressional testimony in November 2007, we presented our preliminary findings on the Food and Drug Administration's (FDA) program for inspecting foreign drug manufacturers.[1] We found that (1) FDA's effectiveness in managing the foreign drug inspection program continued to be hindered by weaknesses in its databases; (2) FDA inspected relatively few foreign establishments; and (3) the foreign inspection process involved unique circumstances that were not encountered domestically.

Our preliminary findings indicated that more than 9 years after we issued our last report on FDA's foreign drug inspection program,[2] FDA's effectiveness in managing this program continued to be hindered by weaknesses in its databases. FDA did not know how many foreign establishments were subject to inspection. Instead of maintaining a list of such establishments, FDA relied on information from several databases that were not designed for this purpose. One of these databases contained information on foreign establishments that had registered to market drugs in the United States, while another contained information on drugs imported into the United States. One database indicated about 3,000 foreign establishments could have been subject to inspection in fiscal year 2007, while another indicated that about 6,800 foreign establishments could have been subject to inspection in that year. Despite the divergent estimates of foreign establishments subject to inspection generated by these two databases, FDA did not verify the data within each database. For example, the agency did not routinely confirm that a registered establishment actually manufactured a drug for the U.S. market. However, FDA used these data to generate a list of 3,249 foreign establishments from which it prioritized establishments for inspection.

Because FDA was not certain how many foreign drug establishments were actually subject to inspection, the percentage of such establishments that had been inspected could not be calculated with certainty. We found that FDA inspected relatively few foreign drug establishments, as shown in table 2. Using the list of 3,249 foreign drug establishments from which FDA prioritized establishments for inspection, we found that the agency may inspect about 7 percent of foreign drug establishments in a given year. At

[1]GAO, *Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, GAO-08-224T (Washington, D.C.: Nov. 1, 2007).

[2]GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: Mar. 17, 1998).

this rate, it would take FDA more than 13 years to inspect each foreign drug establishment on this list once, assuming that no additional establishments are subject to inspection.

**Table 2: Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Market, Fiscal Year 2002 through Fiscal Year 2007**

| | Number of inspections | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Country | FY2002 | FY2003 | FY2004 | FY2005 | FY2006 | FY2007[a] | Total | Number of establishments[b] |
| India | 11 | 19 | 38 | 33 | 34 | 65 | **200** | 410 |
| Germany | 24 | 15 | 35 | 25 | 19 | 22 | **140** | 199 |
| Italy | 17 | 30 | 26 | 21 | 18 | 19 | **131** | 150 |
| Canada | 29 | 12 | 17 | 23 | 23 | 19 | **123** | 288 |
| United Kingdom | 19 | 22 | 15 | 18 | 15 | 13 | **102** | 169 |
| France | 14 | 15 | 13 | 12 | 16 | 24 | **94** | 162 |
| China | 11 | 9 | 17 | 21 | 17 | 13 | **88** | 714 |
| Japan | 11 | 13 | 14 | 21 | 13 | 15 | **87** | 196 |
| Switzerland | 12 | 12 | 11 | 17 | 9 | 14 | **75** | 83 |
| Ireland | 11 | 5 | 11 | 14 | 3 | 11 | **55** | 61 |
| All other countries | 63 | 38 | 63 | 61 | 45 | 80 | **350** | 817 |
| **Total** | **222** | **190** | **260** | **266** | **212** | **295** | **1,445** | **3,249** |

Source: GAO analysis of FDA data.

[a]Inspection data for fiscal year 2007 may not be complete because FDA provided these data as of September 26, 2007, prior to the end of the fiscal year.

[b]This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections.

FDA's data indicated that some foreign drug manufacturers had not received an inspection, but FDA could not provide the exact number of foreign drug establishments that had never been inspected. Most of the foreign drug inspections were conducted as part of processing a new drug application or an abbreviated new drug application,[3] rather than as current good manufacturing practices (GMP) surveillance inspections, which are used to monitor the quality of marketed drugs. FDA used a risk-based

[3]FDA must approve a new drug application before a new drug product may be marketed in the United States; approval for a generic drug is sought through an abbreviated new drug application. FDA also reviews scientific and clinical data contained in the applications, as part of its process in considering them for approval to be marketed.

process, based in part on data from its registration and import databases, to develop a prioritized list of foreign drug establishments for GMP surveillance inspections in fiscal year 2007. According to FDA, about 30 such inspections were completed in fiscal year 2007, and at least 50 were targeted for inspection in fiscal year 2008. Further, inaccuracies in the data on which this risk-based process depended limited its effectiveness.

Finally, the very nature of the foreign drug inspection process involved unique circumstances that were not encountered domestically. For example, FDA did not have a dedicated staff to conduct foreign drug inspections and relied on those inspecting domestic establishments to volunteer for foreign inspections. While FDA may conduct unannounced GMP inspections of domestic establishments, it did not arrive unannounced at foreign establishments. It also lacked the flexibility to easily extend foreign inspections if problems were encountered due to the need to adhere to an itinerary that typically involved multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult to conduct than domestic ones. FDA did not generally provide translators to its inspection teams. Instead, they may have had to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

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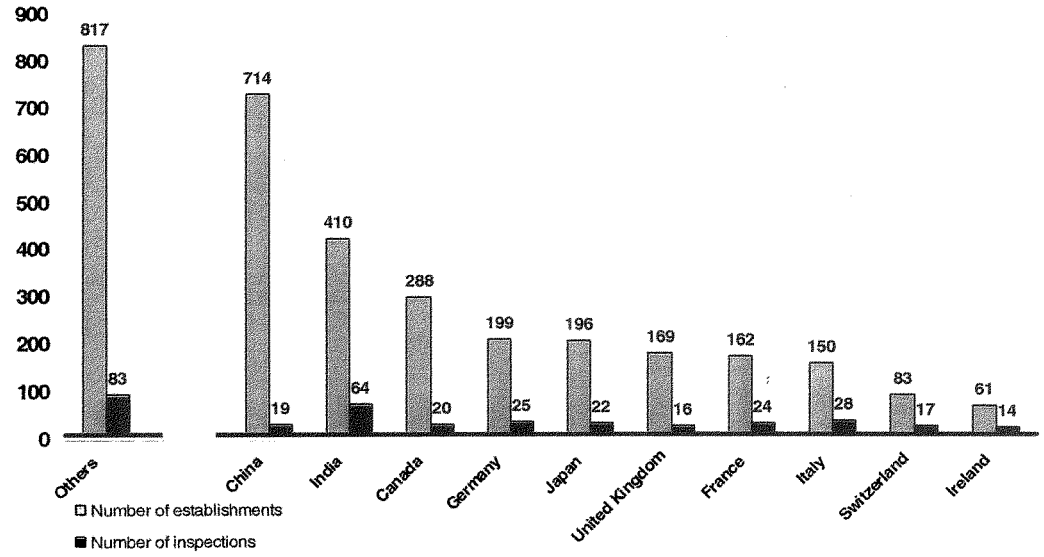
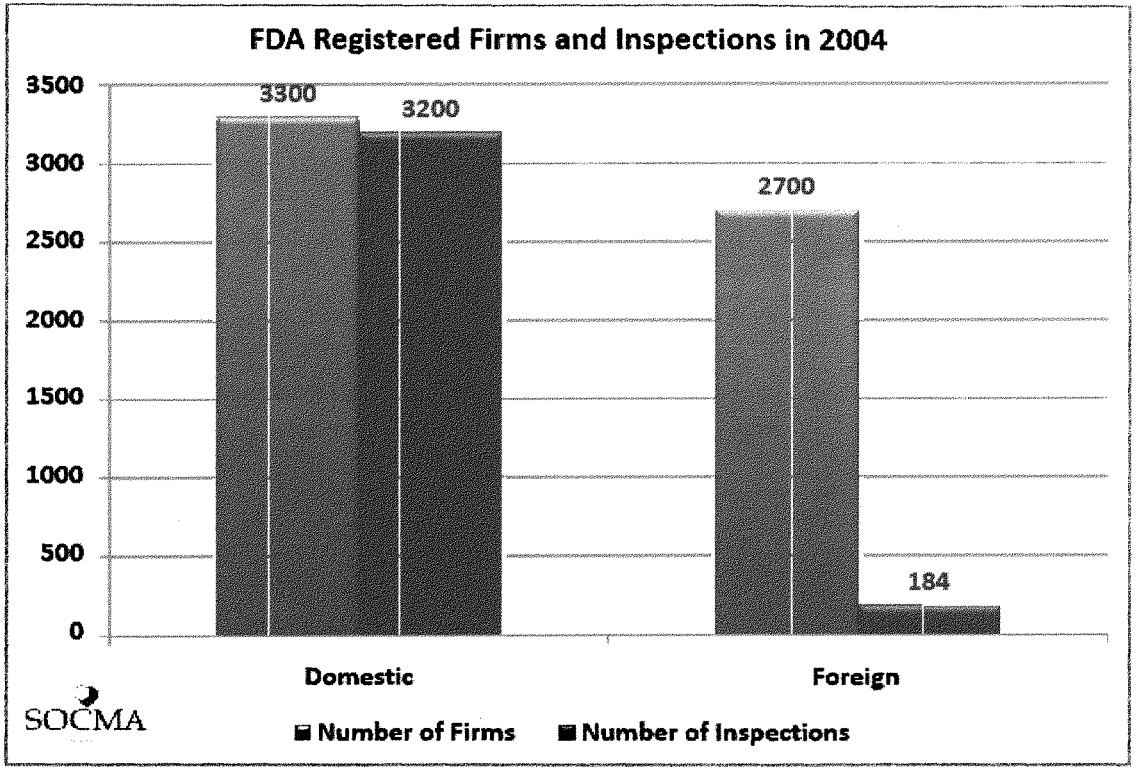
# Number of Foreign Establishments and FDA Inspections, including for the 10 Most Frequently Inspected Countries, Fiscal Year 2007



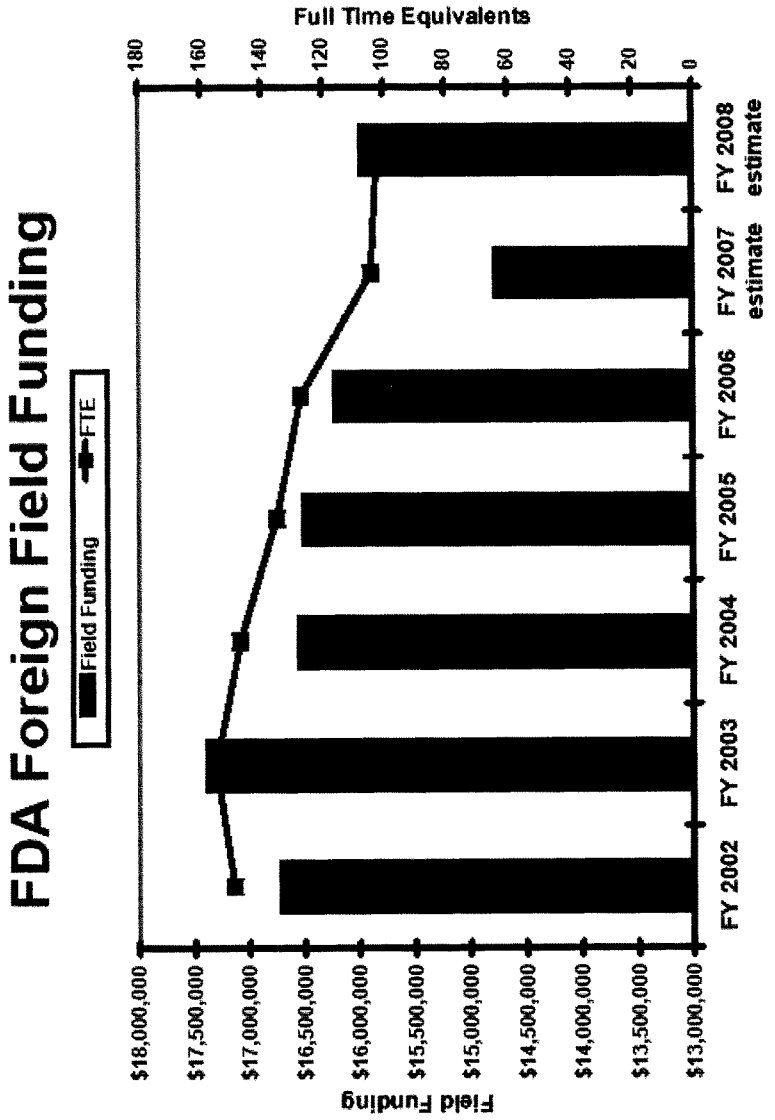

Source: GAO analysis of FDA data.

Average Time Between
FDA Inspections
2.7 yrs
30+ yrs
United States
China




**Number of firms** data taken from the CDER 2005 Compliance Update presented by Kristen Evans at the 29th International cGMP Conference, University of Georgia, March 2005.

**Number of inspections** data taken from the 2004 CDER Report to the Nation published August 2005.




*FDA Data Provided to Committee on Energy and Commerce, October 2007

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# Examples of manufacturer information and MIDs:

**LA VIE DE FRANCE**
243 Rue de la Payees
62591 Bremond, France
Order Date:
Item Number:
Quantity:
Destination:

**MID: FRLAVIE243BRE**

**20TH CENTURY TECHNOLOGIES**
5 Ricardo Munoz, Suite 5880
Caracas, Venezuala
Order Date:
Item Number:
Quantity:
Destination:

**MID: VE20TCEN5880CAR**

**N. MINAMI & CO.,LTD.**
2-6, 8-Chome Isogami-Dori,Fuklai-Ku
Kobe, Japan
Order Date:
Item Number:
Quantity:
Destination:

**MID: JPMINCO268KOB**

| FR | VE | JP | The ISO country code |
|---|---|---|---|
| LA VIE | 20T CEN | MIN CO | The first three letters of the first and the first three letters of the second name of the manufacturer |
| 243 | 5880 | 268 | Up to four numbers from the manufacturer's address, if there are numbers in the address line. Brokers find the largest number on the address line and use up to the first four digits (e.g. If the address is 11455 Main Street Suite 9999, the customs broker would enter "1145" for this section of the MID). |
| BRE | CAR | KOB | The first three letters of the city in which the manufacturer is located |

Source: GAO analysis of Customs and Border Protection information.

GAO

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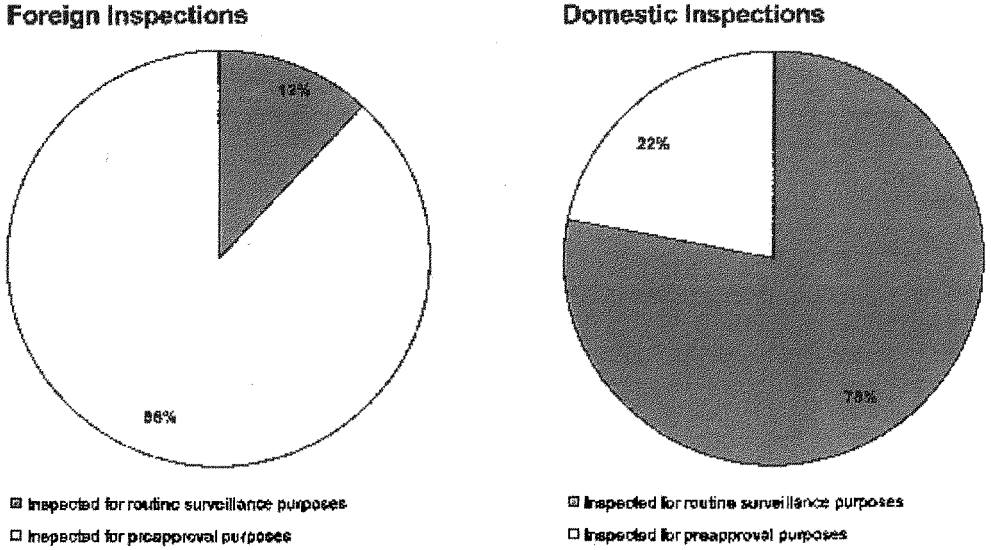
# Foreign and Domestic Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007

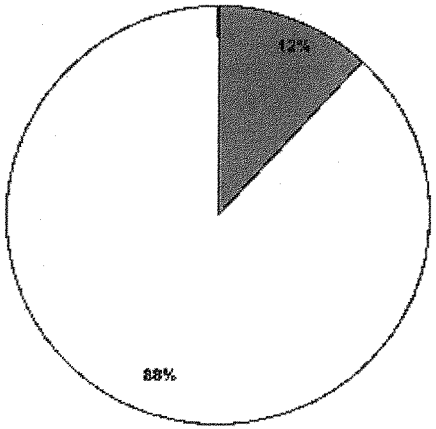



Source: GAO analysis of FDA data.

GAO

# Foreign Preapproval and Routine Surveillance Inspections, Fiscal Years 2002—2007

**Foreign Inspections**




- Inspected for routine surveillance purposes
- Inspected for preapproval purposes

Source: GAO analysis of FDA data.

GAO

# FDA Data Used to Estimate the Number of Foreign Establishments Subject to Inspection

**Drug Registration and Listing System (DRLS):**

- Contains information on about **3,000** foreign establishments registered to manufacture drugs for the United States.
- FDA does not routinely verify the information provided by establishments.

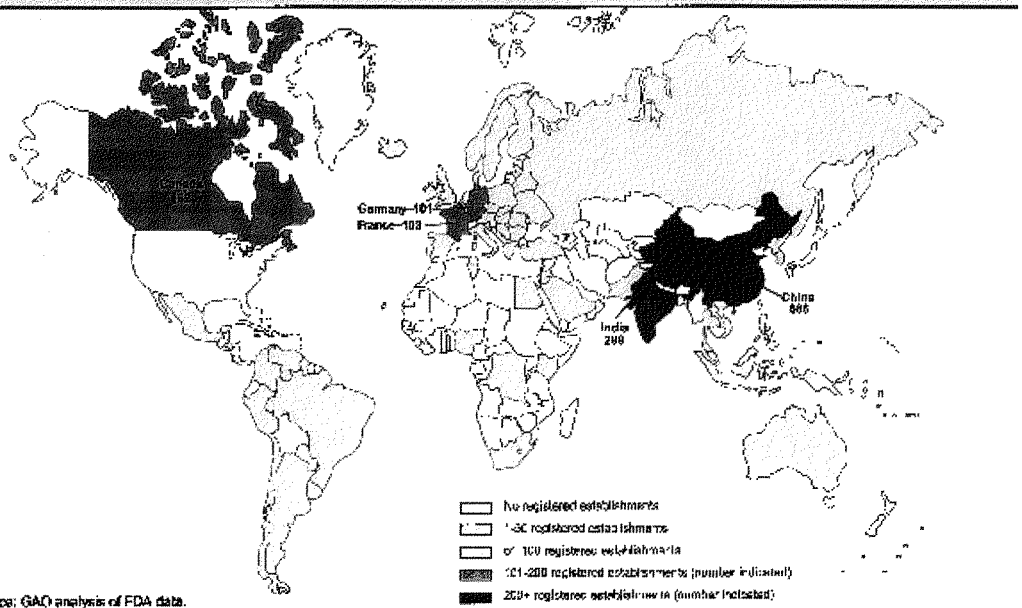
**Operational and Administrative System for Import Support (OASIS):**

- Contains information showing that about **6,800** foreign establishments had drugs imported into the United States.
- OASIS may artificially inflate the number of foreign establishments.

GAO

Accountability * Integrity * Reliability

# Foreign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007




Source: GAO analysis of FDA data.

The New York Times

February 16, 2008

# China Didn't Check Drug Supplier, Files Show

By WALT BOGDANICH and JAKE HOOKER

A Chinese factory that supplies much of the active ingredient for a brand of a blood thinner that has been linked to four deaths in the United States is not certified by China's drug regulators to make pharmaceutical products, according to records and interviews.

Because the plant, Changzhou SPL, has no drug certification, China's drug agency did not inspect it. The United States Food and Drug Administration said this week that it had not inspected the plant either — a violation of its own policy — before allowing the company to become a major supplier of the blood thinner, heparin, to Baxter International in the United States.

Baxter announced Monday that it was suspending sales of its multidose vials of heparin after 4 patients died and 350 suffered complications. Why the heparin caused these problems — and whether the active ingredient in the drug, derived from pig intestines, was responsible — has not been determined.

The plant in Changzhou, west of Shanghai, appears to fall into the type of regulatory void that American and Chinese health officials are trying to close — in which chemical companies export pharmaceutical ingredients without a Chinese drug license.

China provides a growing proportion of the active pharmaceutical ingredients used in drugs sold in the United States. And Chinese drug regulators have said that all producers of those ingredients are required to obtain certification by the State Food and Drug Administration. However, some of the active ingredients that China exports are made by chemical companies, which do not fall under the Chinese drug agency's jurisdiction.

In December, American and Chinese regulators signed an agreement under which China promised to begin registering at least some of the thousands of chemical companies that sell drug ingredients. Some of these companies are the source of counterfeit or diluted drugs, including those used to treat malaria.

Discussions that led to the accord began after an unlicensed chemical plant in China made a tainted drug ingredient that poisoned more than 170 people in Panama, killing at least 115.

The heparin plant in China has not been accused of providing a harmful product. The American majority owner of that plant, Scientific Protein Laboratories, also owns a plant in Wisconsin that produces the active ingredient in heparin for Baxter.

In response to questions, Scientific Protein issued a statement confirming that its Chinese plant had no license from the Chinese agency, but said that its raw ingredients come from a licensed supplier.

The statement added that an "independent private U.S. validation company" had found the plant to be in compliance with good manufacturing practices. And a spokeswoman for Baxter, which buys heparin's active ingredient from Scientific Protein, said it had inspected the China plant less than six months ago.

A spokesman for China's State Food and Drug Administration, Shen Chen, said Friday that "as far as we know, it is not a drug manufacturer — it is a producer of chemical ingredients."

Eric S. Langer, managing partner of BioPlan Associates, which prepares and publishes reports on the biopharmaceutical and biotechnology industry, said he found it hard to believe that a company exporting the heparin ingredient would not be licensed by Chinese drug regulators.

"Being able to produce a pharmaceutical or a biologic in the U.S. or anywhere without having regulatory oversight really doesn't happen," Mr. Langer said, adding, "I find it surprising from a regulatory perspective, and I find it surprising from a business perspective."

Karen Riley, a spokeswoman for the United States Food and Drug Administration, said inspectors from that agency would be visiting the Changzhou plant soon. Ms. Riley said she could not be more specific. Earlier in the week she described her agency's failure to inspect the plant as a "glitch."

Congress has criticized the oversight by the Food and Drug Administration of bulk pharmaceutical ingredients made by foreign manufacturers and sold in the United States. A growing number of those ingredients now come from China. Of the 700 approved Chinese drug plants, the United States agency has inspected only 10 to 20 each year.

Baxter makes roughly half of the United States supply of heparin, which is used widely for surgical and dialysis patients. Problems with Baxter's heparin were first noticed late last year when four children undergoing dialysis in Missouri had severe allergic reactions minutes after being injected with the drug.

The F.D.A. then allowed Baxter to deliver heparin that it was in the midst of shipping, for fear that a total recall would lead to a shortage of the drug, but cautioned doctors to use as little of it as possible and to administer it very slowly.

The agency also suggested that doctors give steroids or antihistamines with the Baxter heparin to help prevent allergic reactions.

Erin Gardiner, a spokeswoman for Baxter, defended Scientific Protein, saying it had been making the heparin ingredient for more than 30 years. "They have been a good supplier," she said.

Although the cause of the adverse reactions has yet to be determined, she said tests performed by her company had detected unspecified differences between some lots of the ingredient. She did not say whether the lots had come from China or from the Wisconsin plant, which Scientific Protein also owns.

Those differences had not turned up in routine testing that the company does on active ingredients, Ms. Gardiner said, but she said Baxter had used "advanced testing techniques" to find the differences. She added that it was unclear whether the finding was significant.

Two Congressional committees have asked the Food and Drug Administration for more information about inspections of plants making the active ingredient of heparin.

*Andrew W. Lehren contributed reporting.*

The New York Times



February 28, 2008

# Twists in Chain of Supplies for Blood Drug

By DAVID BARBOZA and WALT BOGDANICH

RUGAO, China — With reports of more than 400 patients in the United States suffering serious complications after receiving the blood-thinner heparin, American investigators are trying to determine whether the raw material for the drug, made from pig intestines, became contaminated on the journey that begins in the slaughterhouses of China.

The investigators are examining the records of a factory an hour from here that supplies much of the active ingredient in heparin for Baxter International, which earlier this month halted sales of multidose vials of heparin after reports of injuries and four deaths.

The owner of the factory, which is known as Changzhou SPL, says its supply chain is safe. It buys raw material from only two reputable wholesalers, it says, and audits their 10 to 12 suppliers.

"We have a collection chain in place, and we stick with that," said David Strunce, the president of Scientific Protein Laboratories, an American company that owns a majority of Changzhou SPL. He declined repeated requests from The New York Times to identify those smaller suppliers, saying it was proprietary information.

But interviews with dozens of heparin producers and traders in several Chinese provinces, as well as a visit to a village near here dominated by tiny family workshops that process crude heparin from pig intestines, show the difficulties confronting investigators as they seek to trace the supply chain. The picture that emerges is of a chain more complex, and less orderly, than the one Mr. Strunce laid out.

The Chinese heparin market has become increasingly unsettled over the last year, as pig disease has swept through the country, depleting stocks, leading some farmers to sell sick pigs into the market and forcing heparin producers to scramble for new sources of raw material. Traders and industry experts say even big companies have been turning more often to the small village workshops, which are unregulated and often unsanitary.

One of the wholesalers named by Scientific Protein Laboratories, Ruihua Biochemical in Hangzhou, said it provided a mix of crude heparin that it manufactured and some that it bought "from small factories nearby in several villages." The owner, Hua Ruihua, said he never inspected the small factories. "We are not the government," he said in a telephone interview. "We have no right to inspect their pigs or intestines or facilities."

The owner of one of those workshops, Fan Yinan, said, "I sold to Ruihua several times before, but since last September I have had no intestines." He confirmed that "no one from Ruihua inspected my pigs or intestines."

Asked about Ruihua Biochemical, the S.P.L. chief, Mr. Strunce, said, "We have no information to suggest that your information is true."

This week, a spokeswoman for Baxter said the number of reports of adverse reactions to heparin had surpassed 400. A spokeswoman for the Food and Drug Administration in the United States said the agency was reviewing the new reports and did not yet have a revised count.

The authorities have not determined that problems with the heparin supply chain led to the deaths and adverse reactions, first reported last month in Missouri. Nor have investigators determined that heparin from China was the culprit. Baxter also gets some of its ingredients from a plant in Wisconsin. Neither S.P.L. nor Baxter has been accused of doing anything wrong.

Even so, the problems involving heparin have again focused attention on the quality of products from China and the gaps in regulation by both the Chinese and United States governments. S.P.L.'s plant in Changzhou was certified by American officials to export to the United States even though neither government had inspected it. The plant has been exporting heparin to Baxter since 2004.

Like many chemical companies in China that make pharmaceutical ingredients for export, S.P.L. fell into a regulatory void. A spokesman for China's State Food and Drug Administration, Shen Chen, said his agency had not inspected the S.P.L. factory because "as far as we know, it is not a drug manufacturer; it is a producer of chemical ingredients." Mr. Shen said his agency was helping American investigators as part of a recent agreement with American regulators.

The process of making heparin begins with the intestines of slaughtered pigs, from which mucous membrane is collected and cooked, eventually producing a dry substance known as crude heparin. Major heparin producers like S.P.L. take that substance, refine it and sell it to companies like Baxter that make the final product, which is widely used in cardiovascular surgery and dialysis.

Some experts say as much as 70 percent of China's crude heparin — for domestic use and for export — comes from small factories in poor villages. One of the biggest areas for these workshops is here in coastal Jiangsu Province, north of Shanghai, where entire villages have become heparin production centers.

In a village called Xinwangzhuang, nearly every house along a narrow street doubles as a tiny heparin operation, where teams of four to eight women wearing aprons and white boots wash, splice, separate and process pig intestines into sausage casings and crude heparin.

The floors had large puddles and drainage channels; the workshops were dilapidated and unheated; and steam from the production process fogged up the windows and soaked the walls. There were large ovens to cook ingredients and halls lined with barrels to store enzymes, resins, intestines and wastewater.

"This is our family-style workshop," said Zhu Jinlan, the owner of one heparin operation, who stopped sorting pig intestines and invited visitors to a back room, where she lives with her husband and child. "We've been doing this about 10 years."

Experts say the small, unregulated factories could pose dangers because they do not have the same controls

and rules as large slaughterhouses, which also produce crude heparin.

"If you don't control the incoming source, it's very hard to get rid of the contaminants," says Liu Jian, a heparin expert at the University of North Carolina.

Mr. Strunce of S.P.L. says his company never buys directly from the crude-heparin producers, only through its wholesalers, which he called "consolidators" — Changzhou Techpool, its Chinese joint venture partner, and Ruihua. His company, he said, has records documenting all the transactions.

But here in Rugao, producers of crude heparin tell a somewhat different story. A sales manager for a major supplier, Nantong Koulong, said he sells directly to S.P.L. without going through either of the two wholesalers. "We provided crude heparin to Changzhou SPL," said the sales manager, Chen Jianjun. Some of Koulong's stock comes from the unregulated workshops, he said.

The owner of one such workshop, Ms. Zhu in Xinwangzhuang, said she sold to S.P.L. two years ago. She also sells to Koulong. "We are really a traditional family-style plant," she said. "We have no certificate."

S.P.L. said it never bought directly or indirectly from Koulong.

To the south, in Zhejiang Province, two officials of Zhejiang Willing Animal Byproducts Processing said they, too, sold to S.P.L. "We supply heparin to Changzhou SPL," said Fang Weicai, the general manager, although he said later that he sold it privately and not under the auspices of his company.

After an outbreak of blue ear pig disease swept through 25 of China's 31 provinces and regions last year, prices soared, and many drug suppliers had to look to the small workshops. The epidemic, said Cui Huifei, a heparin expert at the Shandong University School of Medicine, "made those biotech companies inevitably purchase from the family-style plants, for cheaper prices."

A sales manager for another large slaughterhouse in Shandong Province, north of Jiangsu, said he was approached late last year by a buyer for S.P.L. offering what he described as rock-bottom prices for crude heparin.

"It was impossible," said the sales manager, Wang Shengfu, who works for Shandong Jinluo Group, a major producer of crude heparin. "Only small factory-style farms could accept that low price."

The deal was never consummated.

Mr. Strunce said S.P.L. responded to the disease outbreak by buying less raw material in China. "We were not out looking for additional heparin because we made do with what we already have," he said, adding that the company "pays more than many people for heparin over there because we require a higher standard of heparin."

*David Barboza reported from Shanghai and Rugao, and Walt Bogdanich from New York. Jake Hooker contributed reporting from Beijing, and Chen Yang contributed research from Shanghai.*

The New York Times



**March 6, 2008**

# Drug Tied to China Had Contaminant, F.D.A. Says

By GARDINER HARRIS and WALT BOGDANICH

WASHINGTON — Federal drug regulators said Wednesday that a critical blood thinner that had been linked to at least 19 deaths and whose raw components were produced in China contained a possibly counterfeit ingredient that mimicked the real drug.

Routine tests failed to distinguish the contaminant from the drug, heparin. Only sophisticated magnetic resonance imaging tests uncovered that as much as 20 percent of the product's active ingredient was a heparin mimic blended in with the real thing. Federal officials said they did not know what the contaminant was.

"At this point, we do not know whether the introduction was accidental or whether it was deliberate," said the Food and Drug Administration's deputy commissioner, Dr. Janet Woodcock.

Heparin is made from pig intestines. Scientific Protein Laboratories, based in Waunakee, Wis., bought raw heparin produced in some cases in small, unregulated family workshops in China and processed it in plants in Wisconsin and China, according to heparin traders and producers in China. Baxter International purchased the active ingredient from Scientific Protein and sold the finished drug.

Wayne Pines, a spokesman for Scientific Protein Laboratories, said that nothing sinister about the contamination had been proved. "There is no evidence of counterfeiting or tampering or anything of that nature," Mr. Pines said. "No one really knows what happened here."

Beginning in November, public health officials received reports of patients experiencing severe allergic reactions after being given Baxter's product. Baxter initiated a series of recalls that culminated last week in a withdrawal of nearly all of Baxter's heparin production.

The F.D.A. has now received 785 reports of serious injuries associated with the drug's use. Forty-six deaths have also been reported to the agency, but Dr. Woodcock said that just 19 of these appeared related to the suspect heparin. Baxter executives said that the total death toll was actually four.

APP Pharmaceuticals, which previously split the heparin market with Baxter, has been ramping up production to meet demand. So far, APP's products show no signs of similar contamination, Dr. Woodcock said, although some of APP's production is also based in China.

Most of the world's heparin supply originates in China, according to Baxter. The F.D.A. will soon make public the test used to distinguish between real heparin and its mimic in hopes that regulatory bodies around the world will adopt the test. "We don't know if any of the heparin products worldwide might contain this contaminant, and that is something we are going to be looking into," Dr. Woodcock said.

The F.D.A. has yet to prove that the heparin contaminant is the cause of the deaths and illnesses now associated

with the use of Baxter's product. But heparin batches associated with illnesses, all of which were produced with ingredients made in China, were found to contain the contaminant while batches not linked to illnesses proved to be untainted. In a written statement, Scientific Protein said that "it is premature to conclude that the heparin active pharmaceutical ingredient sourced from China and provided by S.P.L. to Baxter is responsible for these adverse events."

Since tainted batches were produced by Scientific Protein's plants in both Wisconsin and China, "either both plants have problems with processing or there's something wrong further up the stream," said Peter Arduini, president of Baxter's medication delivery business.

The F.D.A. admitted last month that it had violated its own policies by failing to inspect Scientific Protein's China plant before approving the drug for sale. The agency sent inspectors to the plant last month who found that at least some heparin was made from "material from an unacceptable workshop vendor."

Baxter undertook its own inspection of the China plant last fall. "A few of our observations touched on the same areas as F.D.A.'s inspectional findings," said Ray Godlewski, vice president for quality at Baxter's medication delivery business. Mr. Godlewski refused to be more specific because, he said, of a confidentiality agreement with Scientific Protein.

Mr. Pines of Scientific Protein said he did not know what problems Baxter uncovered last fall or why those problems were not corrected by the time federal inspectors arrived last month.

China has become by far the largest supplier of pharmaceutical ingredients in the world, but there is growing concern about the quality of the products made there. Last year, the F.D.A. discovered that a pet food ingredient shipped from China contained toxic levels of melamine, which was added to make it appear higher in protein. Many pets became ill, and some died.

In addition, Panamanian investigators have concluded that at least 174 people were poisoned, 115 of them fatally, by counterfeit cold medicine linked to an unlicensed Chinese chemical plant.

A series of independent assessments, including one by the agency's own Science Board, have found that the F.D.A. is increasingly overwhelmed by its many responsibilities and is incapable of protecting the public from unsafe drugs, medical devices and food — particularly from China.

The Government Accountability Office recently discovered, for example, that over a six-year period, the F.D.A. inspected just 64 of the nearly 700 medical device plants registered in China. Medical devices can include items like stents and spinal screws.

There is a growing bipartisan consensus on Capitol Hill that the agency needs a rapid infusion of money. The Bush administration has proposed an increase in the agency's budget next year of just 3 percent — not enough to keep up with increased expenses. But the F.D.A. commissioner, Dr. Andrew C. von Eschenbach, said in a recent interview that the agency needed more money.

Dr. von Eschenbach said Wednesday that, even if the agency had adequately inspected the China plant, it might not have caught a problem resulting when "someone either intentionally or unintentionally manipulates a product." He said that the agency needed to approach its inspections program "in a more strategic way" and that

it needed "good surveillance" of adverse events associated with unsafe drugs "so that we can respond and mitigate that outcome."

But the F.D.A. has for years had a drug safety surveillance system that relies on voluntary reports by patients and doctors to report problems. The agency itself estimates that these reports represent as little as 1 percent of the actual number of drug problems.

Problems with heparin reported to the agency include difficulty breathing, nausea, vomiting, excessive sweating and rapidly falling blood pressure that in some cases led to life-threatening shock.

The Chinese heparin market has been in turmoil over the past year as pig disease swept through the country, leading some farmers to sell sick pigs into the market and forcing heparin producers to scramble for new sources of raw material.

*Gardiner Harris reported from Washington, and Walt Bogdanich from New York.*

The New York Times



**March 20, 2008**

# Heparin Find May Point to Chinese Counterfeiting

By WALT BOGDANICH

Federal drug regulators, in announcing Wednesday that the mystery contaminant in heparin was an inexpensive, unapproved ingredient altered to mimic the real thing, moved closer to concluding that Americans might be the latest victims of lethal Chinese drug counterfeiting.

The finding by the Food and Drug Administration culminated a worldwide race to identify the substance discovered early this month in certain batches of heparin, the blood-thinning drug that had been linked to 19 deaths in the United States and hundreds of allergic reactions.

The contaminant, the regulators said, is a chemically altered form of chondroitin sulfate, a dietary supplement made from animal cartilage that is widely used to treat joint pain. The agency's announcement followed a report Wednesday in The New York Times that was the first publicly to identify the modified substance as the likely contaminant. That report was based on nearly two dozen interviews with researchers and scientists in China, the United States and Canada.

Federal officials stopped short of saying that the contaminant — constituting as much as 50 percent of the active ingredient in heparin — was counterfeit. "At the moment we don't know definitely whether the contaminant was introduced intentionally or by accident," said Dr. Janet Woodcock, director of the Food and Drug Administration's center for drug evaluation and research.

Even so, the authorities left little doubt that they believed that the contaminant was not an unintended byproduct of some manufacturing process.

In its natural state, chondroitin sulfate does not have anticlotting properties. But it mimics heparin when altered to form what is called oversulfated chondroitin sulfate. That is what made it difficult for Baxter International, the manufacturer of the heparin associated with the allergic reactions, to detect the impurity. "This compound to our knowledge is not naturally occurring," Dr. Woodcock said. "It should not be in heparin. And it obviously should not be in the form it is in."

While identifying the contaminant was a significant breakthrough, investigators still do not know if it is responsible for causing the allergic reactions. Nor do they know why the modified ingredient ended up in heparin, though they have raised the possibility that the substance was used as cheap filler.

"The base compound, chondroitin sulfate, is very abundant and an inexpensive compound," said Moheb Nasr, director of the agency's office of new drug quality and assessment. Chemically modifying it, Mr. Nasr added, "will not be that expensive either."

The F.D.A. said it had found the contaminated heparin at Changzhou SPL, the Chinese plant that supplies the active ingredient to Baxter. Changzhou in turn buys its heparin from two companies, called consolidators, that

gather crude heparin from workshops that make it from pig intestines.

Many workshops that make crude heparin are unregulated family operations.

Erin Gardiner, a spokeswoman for Baxter, said Wednesday that tests found the supplies were contaminated before they arrived at the Changzhou plant. "The consolidators and workshops handle the crude material, so that is where our focus is turning," Ms. Gardiner said.

So far, Ms. Gardiner said Baxter's investigators had been denied access to the consolidators and workshops. "We will continue to seek access."

Last week, the F.D.A. said it had not yet visited the workshops.

Some heparin producers in China also sell chondroitin sulfate, which can be derived from pig cartilage. Traders and producers say it is far cheaper than heparin, as little as one-twentieth the cost. That could be an enticement for counterfeiters, especially in the wake of a virulent pig virus that swept across China last year, substantially reducing the availability of the starting materials needed to make the active ingredient in heparin.

Contaminated heparin sourced from China has also turned up recently in Germany, where about 80 allergic reactions have been reported. But investigators there have yet to identify the contaminant. F.D.A. officials said their discovery of chemically modified chondroitin sulfate came exactly one year after the discovery that a pet food ingredient shipped from China contained toxic levels of melamine, which was added to make it appear higher in protein. Many pets became ill, and some died.

Around the same time, The Times reported that an unlicensed Chinese chemical plant sold a cheap counterfeit ingredient, diethylene glycol, that was mixed into cold medicine in Panama, killing nearly 120 people and disabling dozens more.

Diethylene glycol mimics its more expensive chemical cousin, glycerine, a safe ingredient used in medicine, food and toothpaste.

The F.D.A. said its search for answers in the heparin case had been made easier because of the cooperation it had received from China's State Food and Drug Administration. That was not the case when United States officials inquired last year about the melamine and diethylene glycol.

The agency cited an accord signed in December by the governments of China and the United States as one reason for the cooperation they had received recently, which they said allowed American investigators to quickly begin their investigation of the additive.

Baxter has recalled virtually all of its heparin products. The F.D.A. has also asked that all heparin entering the country be stopped and tested for the contaminant. Heparin is commonly used in dialysis and cardiac surgery. "We feel doctors and patients can be confident that the product on the market for the large volume uses of heparin, for dialysis and so forth, has been tested and is safe," Dr. Woodcock said.

*David Barboza contributed reporting from Shanghai, and Jake Hooker from Beijing.*

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The New York Times ROCK 'N ROLL WILL NEVER DIE

April 10, 2008

# Heparin Is Now Suspected in 62 Fatalities Across U.S.

By WALT BOGDANICH

The number of suspicious deaths in the United States linked to the blood thinner heparin has risen to 62 from 19, with most of them reported this past December, January and February, according to the first detailed analyses of heparin fatalities by the Food and Drug Administration.

The F.D.A. is still investigating whether those deaths and hundreds of allergic reactions were caused by a heparinlike contaminant made in China that was added to the drug somewhere during the manufacturing process.

The drug agency defined suspicious deaths as those involving one or more allergic reactions or a drop in blood pressure. There have been no reports of deaths since the end of February, after Baxter International recalled heparin made with ingredients from a Chinese supplier.

The agency's Web site reported Tuesday that the 62 deaths covered a 14-month period that began in January 2007. In comparison, the agency said, there were three suspicious deaths involving heparin in all of 2006.

The F.D.A. had earlier identified the contaminant as a chemically altered substance that slipped through standard testing screens because it mimicked heparin. The agency was able to spot the additive only by using a more sophisticated test.

Investigators have not yet established how or why the additive, called oversulfated chondroitin sulfate, ended up in heparin, though the fact that it is cheaper to make than the actual drug points to the possible involvement of counterfeiters.

In addition to Baxter, companies that have recalled heparin products made with Chinese ingredients include Covidien, formerly Tyco Healthcare, and B. Braun. Both Covidien and Braun said that they had received no reports of adverse reactions from the heparin and that the recalls had been undertaken merely as a precaution.

Similar recalls of the drug have occurred in Germany, Denmark, France, Italy and Japan.

Heparin is made from the mucous membranes in pig intestines. It is commonly used in dialysis and in many types of surgery.

Drug regulators in China, the world's biggest supplier of heparin ingredients, have said they are tightening supervision over production of the drug, which involves thousands of small family workshops that gather and treat the raw material from pig intestines.

THE WALL STREET JOURNAL. ONLINE

FORMAT FOR PRINTING sponsored by TOSHIBA Leading Innovation >>

March 10, 2008

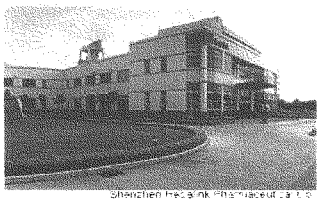
# How Heparin Maker in China Tackles Risks

## Plant Now Supplying U.S. Must Make Frequent Checks To Monitor Difficult Market

By GORDON FAIRCLOUGH
*March 10, 2008; Page B1*



SHENZHEN, China -- Inside Shenzhen Hepalink Pharmaceutical Co.'s high-tech factory in this southern China boomtown, workers in blue protective suits, surgical masks and gloves produce the active ingredient for heparin, the widely used blood-thinning medication.



The Shenzhen Hepalink plant

Since a recall by **Baxter International** Inc. linked to tainted heparin from a different maker in China, Shenzhen Hepalink is the U.S.'s main supplier of the active ingredient in "large-dose" heparin, the type administered during heart surgery and kidney dialysis. It sells to **APP Pharmaceuticals** Inc., Baxter's main rival in the U.S. heparin market.

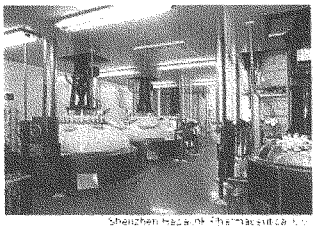
The Shenzhen Hepalink plant has been inspected and approved nine times in recent years by government health authorities, including the U.S. Food and Drug Administration, China's drug watchdog and German regulators. Buyers have done their own audits 25 times. To track a process that starts with crude heparin extracted from pig intestines, the company keeps more than 300 pages of data for each batch to "ensure traceability of each lot," Shenzhen Hepalink Chairman Li says.

Intense scrutiny of the supply chain and strict adherence to government-certified manufacturing practices are essential, he says. "Without this, there are huge risks in production."

The recent problems with heparin from China highlight the difficulty of monitoring the often diffuse and poorly regulated supply chains there -- for both Chinese drug makers and the multinational pharmaceutical companies that buy from them.

China's drug industry, now the world's biggest producer of active pharmaceutical ingredients, has come under heightened scrutiny following deaths and illnesses in the

U.S. that led to Baxter's recall, and allergic reactions in Germany also connected to heparin from China. The problem is similar to last year's discovery of U.S. imports of tainted products including toothpaste, toys and pet food from China. But with medicines, the safety risks are especially big, and the ability to trace ingredients is even more critical to authorities' efforts to pinpoint the cause of adverse reactions and act quickly to limit further ill effects.



Reactor vessels used in the process of purifying crude heparin

The FDA says it found significant amounts of a contaminant in the heparin active ingredients used by Baxter, which came from Scientific Protein Laboratories LLC of Wisconsin and that company's China joint venture, Changzhou SPL. It is still unclear what the contaminant is and how it ended up in the heparin. It is also unclear whether the contaminant is the cause of patients' allergic reactions to Baxter's heparin.

Changzhou SPL registered itself in China as a chemical manufacturer rather than a drug company. As such, it doesn't fall under the jurisdiction of China's State Food and Drug Agency. The U.S. FDA, in an oversight, also failed to inspect the facility when it began making the active ingredient for the U.S. market.

But inspections don't always eliminate problems. China's SFDA approved the two Chinese companies that made the active ingredient for the heparin now recalled in Germany: Changzhou Qianhong Bio-Pharma Co. and Yantai Dongcheng Biochemicals Co. Both companies have declined to comment. The SFDA didn't respond to phone calls for comment on Friday.

The U.S. FDA says it has tested heparin from Shenzhen Hepalink and found no sign of the contaminant discovered in Baxter's ingredient supplies, and APP says it has received no reports of adverse reactions to its heparin.

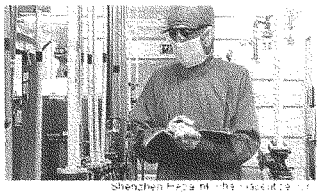
Shenzhen Hepalink's Mr. Li started in the heparin business 24 years ago, setting up an operation in Chongqing in southwest China. In 1998, he says, he started building the more-sophisticated Shenzhen factory, designing it from the ground up to pass tough FDA standards. Getting the hardware right, he says, was only part of the battle. The more difficult task was to build a corporate culture of strict adherence to the myriad rules meant to ensure quality and safety.

The process of heparin production has a grisly start in workshops that extract crude heparin from the intestines of slaughtered pigs. These crude heparin producers operate with essentially no oversight by Chinese health authorities. Many are small, rudimentary operations in farming communities.

The output of these heparin producers is bought up by trading companies, and may change hands several times before it ends up with consolidators who sell it in bulk to drug companies.

For the heparin supplied to Baxter, Changzhou SPL says that it relied on two wholesalers who bought heparin from six to 12 smaller workshops. Scientific Protein says it can trace supplies back to the slaughterhouses where the workshops got their raw materials.

Shenzhen Hepalink says it can trace the crude heparin it



A worker at Shenzhen Hepalink monitors the production of heparin for use as the active ingredient in blood-thinning medicines.

uses back to specific groups of pigs. It deals only with suppliers who get pig innards from government-regulated slaughterhouses and follow strict rules to minimize contamination. A key step, Mr. Li says, is stationing Shenzhen Hepalink employees in quality-assurance labs on the premises of each supplier whose material is destined for the U.S., to make sure his company's rules are followed.

This kind of direct oversight can be important in China, where enforcement is often spotty even in regulated businesses. Crude heparin manufacturers describe enormous variations in everything from record-keeping to what animals they use. They say that rising prices for pigs in China has prompted some crude suppliers to cut corners.

Wang Xiangyang, a factory director at the Zhaoyang Intestine & Casing Factory in Shandong, for instance, says his company has been forced to use sheep innards in addition to pig intestines because of a shortage of pig supplies. "We can't get enough pig intestines," Mr. Wang says. "There are a lot of people around who need them."

The U.S. and Europe stopped using heparin extracted from sheep and cow organs more than a decade ago after scientists became concerned about bovine spongiform encephalitis, or mad-cow disease, and a similar disorder in sheep known as scrapie. The fear was that prions, the tiny particles that cause these devastating illnesses, could be transmitted to humans through ingredients derived from cows or sheep.

Other crude-heparin makers say they suspect that to cut costs, some in the industry have used intestines from pigs infected with a virus, commonly known as blue-ear disease, that has been widespread in Chinese swine herds since mid-2006. Those animals are supposed to be destroyed and not used for food or drug production.

If the companies that buy this crude heparin for use in drugs don't know what potential impurities there are in the raw materials they buy, they may not use the proper measures to remove them, scientists say. Scientific Protein says that it tests all crude heparin to make sure it is from pigs and doesn't contain heparin extracted from sheep or other animals.

At its plant, Shenzhen Hepalink uses three steps -- involving chemical and physical processes -- to remove or deactivate all known pig viruses mixed in with the heparin. These measures have been checked by an independent German lab.

Some of "the products we make are directly injected into people's bloodstreams," says Mr. Li. "So we have great responsibilities."

When FDA officials last month toured the Changzhou SPL factory at the center of Baxter's heparin recall, they described findings that indicated flaws in record-keeping and a lack of evidence that appropriate steps were being taken to effectively rid crude heparin of possible contaminants.

An inspection report released by the FDA late last month says that Changzhou SPL's processes for the "repeated and efficient removal of impurities" have "not been evaluated" to determine their

effectiveness. The report also says that "manufacturing instructions" followed at the plant were "incomplete."

Baxter audited Changzhou SPL in September, Baxter spokeswoman Deborah Spak says. Baxter officials made "several observations," including "a few touching on the same areas" as those identified by the FDA.

Ms. Spak says Baxter approved the Changzhou SPL factory for heparin production "pending satisfactory responses" to the concerns its officials raised. Changzhou SPL provided those responses in January, she says, and Baxter continued to buy its heparin.

**--Ellen Zhu in Shenzhen and Thomas M. Burton in Chicago contributed to this article.**

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March 20, 2008

# FDA Identifies Contaminant in Heparin Batches

By ANNA WILDE MATHEWS and THOMAS M. BURTON
*March 20, 2008; Page A4*

A contaminant found in recalled batches of the blood-thinner heparin was deliberately altered in a way that mimicked the real drug, the Food and Drug Administration said, a finding that will add to pressure on U.S. regulators and pharmaceutical companies to step up oversight of burgeoning Chinese drug production.

- **The News:** The FDA said a contaminant found in recalled batches of the blood-thinner heparin appeared to have been deliberately altered in a way that mimicked the real drug.
- **The Backdrop:** The problem seems to be linked to a heparin ingredient that comes from China.
- **The Upshot:** Pressure is increasing on the FDA and drug makers to ramp up their oversight of Chinese pharmaceutical-ingredient manufacturers.

Yesterday, the FDA said the contaminant, which has surfaced in batches of heparin made from active ingredient sourced in China, appears to be a chemically altered material derived from a cheap and widely available substance found in animals, particularly in cartilage.

The agency said it isn't clear if the contaminant, called over-sulfated chondroitin sulfate, is the cause of allergic reactions, some fatal, that occurred in people who took heparin supplied by **Baxter International** Inc., which has recalled the drug batches linked to the problem. The contaminant has been found in heparin taken by people who had reactions.

Janet Woodcock, the director of the FDA's drug center, said agency investigators aren't sure how the substance got into the heparin. "We cannot rule in or out whether this is accidentally or deliberately introduced into the product," she said.

However, Dr. Woodcock said the contaminant seems to have been deliberately processed by adding more sulfate. She said the "compound to our knowledge is not naturally occurring" and "didn't come straight from the pig." Heparin is derived from pig intestines.

An FDA official noted that chondroitin sulfate is "abundant and cheap," and the chemical processing required to add the extra sulfate "will not be that expensive either." The agency said the substance is likely to be less expensive than actual heparin, but FDA officials "do not have any further data to estimate the cost after the sulfation process." In some samples of Baxter's active ingredient, the contaminant made up between 2% and 50% of the total material, Dr. Woodcock said.



**FURTHER READING**

Heparin Faces Tougher Testing[3]
03/15/08

Heparin Contaminant Is Found[4]
03/06/08

China Says Drug Checks Are Up to Importers[5]
02/28/08

Gaps Found in Chinese Drug Supply Chain[6]
02/21/08

Academic experts said the process of adding sulfate was likely one that would require at least a basic chemical manufacturing facility. The extra sulfate would make the chondroitin sulfate more chemically similar to heparin, and it could have clumped together with the actual heparin in a way that would make it difficult to detect through most standard processing, said Jian Liu, an associate professor at the University of North Carolina, Chapel Hill.


Charles E. Grassley

The disclosure immediately drew concern from Congress. Democratic Reps. John Dingell and Bart Stupak of Michigan said they planned a hearing about heparin next month. Democratic Sen. Edward Kennedy of Massachusetts said "it is unacceptable that Americans have died and been seriously injured by what appears to be deliberate tampering." Sen. Charles Grassley, an Iowa Republican, said the investigation has "provided additional evidence of the need for a robust foreign inspection program within the Food and Drug Administration."

Last year, the FDA blocked all toothpaste from China at the U.S. border for testing after reports that authorities found diethylene glycol, a chemical used in products such as antifreeze, in toothpaste in Panama and other countries. In addition, wheat flour from China that was used in some pet food was found to contain melamine, an industrial chemical. The substance was blamed for pet illnesses and deaths.

The FDA recently announced that it had received permission from the State Department to place eight staffers in China, but its plans were pending authorization from the Chinese government. In fiscal 2007, there were a total of 714 Chinese facilities making drugs or drug ingredients for the U.S. market.

Counterfeit drugs and ingredients have been an increasing worry for the FDA. In fiscal 2007, the FDA opened 31 domestic counterfeit-drug investigations, which can involve products with ingredients made overseas. There were 54 in 2006 and 32 in 2005. In 1997, there were just nine.

In a statement, the trade group Pharmaceutical Research and Manufacturers of America said "brand-name pharmaceutical companies work closely with foreign and domestic manufacturers of [active pharmaceutical ingredients] to help ensure that extensive regulatory requirements are met to protect patient health."

Baxter and supplier Scientific Protein Laboratories LLC of Waunakee, Wis., both said yesterday the contaminant seems to have been introduced into the heparin at its crude stage, before it arrived at Scientific Protein's Chinese joint venture Changzhou SPL for processing into active ingredient. Both Baxter and a consultant working with Scientific Protein said the substance appears to be derived from pig tissue.

A Baxter spokeswoman said the company is focusing its investigation on "consolidators and workshops" in China, and added that "consolidators are a bit more sophisticated" in chemical expertise. Baxter said Scientific Protein uses three consolidators but won't say whether the adulterant is present in lots from one, or two, or all three of its consolidators.

The FDA has received reports of hundreds of reactions and 19 deaths of patients after taking heparin. Heparin sold in Germany by Rotexmedica GmbH, a unit of the French company Groupe Panpharma, also has been recalled. Baxter and Rotexmedica relied on different Chinese suppliers.

A professory of pathology and pharmacology at Loyola University Medical Center near Chicago, Jawed Fareed, said "the presence of this contaminant clearly shows a deliberate attempt to increase the yield of heparin."

**Write to** Anna Wilde Mathews at anna.mathews@wsj.com[1] and Thomas M. Burton at tom.burton@wsj.com[2]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

APR 2 1 2008

**Warning Letter**

**Via FedEx and facsimile**

**WL: 320-08-01**

Dr. Yan Wang, Ph.D.
General Manager
Changzhou SPL Company, Ltd (a/k/a "Kaipu")
3 Changhong West Road
Hutang Township, Wujin City
Changzhou
China

Dear Dr. Wang:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your active pharmaceutical ingredient manufacturing facility in Wujin City, Changzhou, China by U.S. Food and Drug Administration ("FDA") Investigator Regina T. Brown and Chemist Zi Qiang Gu on 20-26 February 2008. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) in the manufacture of active pharmaceutical ingredients (API). These deviations were listed on an Inspectional Observations form (FDA-483) issued to you at the close of the inspection.

These CGMP deviations cause your API to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)]. This section of the Act states that drugs, as defined in the Act, are adulterated when the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drugs meet the requirements of this Act as to safety and have the identity and strength and meet the quality and purity characteristics, which they purport or are represented to possess.

Our review included your March 17, 2008 and April 15, 2008 written responses to the FDA-483 observations. We note that some corrections appear to have been implemented and that you have promised that others will soon be implemented. However, your response

does not adequately address some of the deficiencies, as further discussed below. Specific areas of concern include, but are not limited to:

1. **There is no assurance that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities.**

Our inspection disclosed that your firm lacked an adequate evaluation of the effectiveness of critical processing steps designed to remove impurities, and critical process parameters were not well defined or controlled (observation #1 of the FDA-483). The inspection also found that an impurity profile has not been established for the heparin sodium API (observation #2 of the FDA-483).

In your March 17, 2008, response to observation #1, you state that the firm has conducted two successful process validation studies, one in 2002 and one in 2004. However, the validation studies failed to determine whether the process was capable of adequately removing identified and unidentified impurities. Your response does not include data to demonstrate that your process will consistently remove impurities, and your firm continues to lack established impurity limits for the API. It is essential that your firm establish that controls are in place for assuring the consistent performance of the processing steps to remove impurities in order to ensure the identity, quality and purity of the drugs your firm produces.

In your response, your firm acknowledges certain deficiencies in providing evaluations of critical processing steps. Please provide data from validation studies that assess whether the process is capable of consistently removing impurities, and your evaluation of the reliability of the controls used to establish and monitor performance of the processing steps.

In your March 17, 2008, response to observation #2, you state that the current testing regimen for heparin sodium is consistent with industry practice reflected in the ICH Q7A Guidance (Laboratory Controls, Testing of Intermediates and APIs) which states that "Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin." Although a full impurity profile may not be necessary as part of the batch-to-batch testing of certain APIs, it is necessary that specifications for impurities be established for the production of all API and that each API batch be tested for conformance to these specifications. The ICH Q7A Guidance (Laboratory Controls, General Controls) states that appropriate specifications should be established for APIs, including for control of impurities. Your firm failed to establish appropriate specifications for identified and unidentified impurities for the heparin sodium API. Your firm also failed to perform adequate tests to detect impurities in this API.

In your March 17, 2008, response to observation #2 your firm also states that the complexity of the investigation into the recent heparin product recalls demonstrates the

difficulty of isolating and identifying impurities in heparin due to the nature of the [ ] mixture of [ ] However, the mere fact that it is difficult to isolate and identify impurities is insufficient rationale for not establishing appropriate specifications for, and routinely monitoring, impurities during production. In fact, we note that you committed in your response to include an "impurity profile update" in each DMF annual report.

Please note that it is essential for your firm to establish appropriate specifications and adequate testing to ensure the consistent removal of undesirable impurities, including those that are potentially harmful to human health.

It is your responsibility to ensure that your API meets the identity, quality and purity characteristics that it is represented to possess.

2. **You fail to have adequate systems for evaluating the suppliers of heparin crude materials, and the crude materials themselves, to ensure that these materials are acceptable for use.**

Our inspection found (Observation #6 of the FDA-483) that you received lots of material from an unacceptable workshop vendor that were used in your API. In your March 17, 2008, response to observation #6, your firm acknowledges inadequacies in the firm's supplier qualification efforts. For example, you state that the firm received and used heparin crude materials from a workshop that had been designated by your firm in a "pre-audit" as "unacceptable" and that was ultimately not approved by your firm. Your firm used this crude material in the production of API lots that were shipped to the United States.

Your system for evaluating suppliers of crude heparin material is ineffective to ensure that materials are acceptable for use. As described above, your firm accepted and used heparin crude material from a supplier that you had preliminarily determined was unacceptable. Your system failed to verify that the supplier was acceptable prior to the use of the crude material. Furthermore, after your firm determined that the supplier was not acceptable, your firm failed to take any corrective action with respect to the processed raw material.

All raw materials that are received and used in producing heparin sodium API should be qualified using a system to ensure that raw materials are of acceptable identity, quality and purity before use. It is important to establish appropriate specifications for these materials and to assure your suppliers provide materials meeting these specifications. These specifications should be approved by the quality unit. Your firm has failed to establish appropriate specifications for your incoming crude materials.

Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.

3. **The test methods performed for heparin sodium USP have not been verified to ensure suitability under actual conditions of use.**

Our inspection found (Observation #4 of the FDA-483) that you have not ensured that certain USP compendial test methods were verified under actual conditions of use. Specifically, you have failed to conduct adequate verification of USP compendial test methods as applied to the production of your firm's API. The data you provided in your March 17, 2008, response did not include information about the suitability, accuracy, and detection limits of certain test methods for API, such as the protein test method, used by your firm. There was no indication from these data that your firm's test methods could reliably detect and quantify the presence of proteins in the finished API. In addition, your firm had not conducted suitability testing of the method to determine the limit of detection for the method. The suitability for use of the protein method for in-process testing was also not established.

In your March 17, 2008, response to the FDA-483, you state that the firm has conducted suitability tests. In addition, you state that the test method was not verified because it was a basic compendial test. You assert that USP <1226>, Verification of Compendial Procedures, states that verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. In your response, you also state that the laboratory performed basic suitability testing on the heparin sodium API analytical method in accordance with your standard operating procedures (SOPs).

We disagree with your assertions that verification is not required for those USP test methods used by your firm. In accordance with cGMP, analytical methods should be validated unless the methods used are included in a relevant pharmacopoeia or other recognized standard reference. If the method is a compendial method, verification of the methods should be conducted to determine that the method is suitable for its intended use under actual conditions. We acknowledge that the USP informational chapter <1226> suggests that there is a lesser need for verification for the simplest tests such as loss on drying, residue on ignition, and pH measurements. However, these do not include the test methods at issue, including the protein test method.

Further, the ICH Q7A guidance (Good Manufacturing Practices for Active Pharmaceutical Ingredients) at section 12.8 "Validation of Analytical Methods" states clearly that "the suitability of all testing methods used should nonetheless be verified

under actual conditions of use and documented." Thus, although it is not necessary to validate USP test methods, it is necessary to verify that these USP methods are suitable for the specific conditions of use. Furthermore, the suitability tests you describe in your response do not verify that the USP tests are suitable for the specific conditions of use.

Please provide data that demonstrate that the compendial test method has been verified and determined to be suitable under actual conditions of use.

4. **Equipment used to manufacture heparin sodium USP is unsuitable for its intended use.**

Our inspection team observed (Observation #7 of the FDA-483) that equipment tanks used in the final [ ] step were constructed of [ ] These tanks were identified as clean. However, unidentified material was observed adhering to the inside surfaces of tanks. It was also observed that surfaces of the tank were scratched, not smooth. We also note that volume markings on the outside of the [ ] tanks had tape adhered to it with markings. In addition, the cleaning method used for cleaning these tanks was not qualified.

There should be written procedures for cleaning of equipment. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Acceptance criteria should be established and cleaning procedures should be defined and evaluated.

In your response to observation #7, you stated that the [ ] tanks used in the final [ ] step will be replaced with [ ] This [ ] will be equipped with clean-in-place system and an automated level reader. Until the new tanks arrive, you state that you will replace the existing [ ] tanks with new [ ] tanks and conduct cleaning validation on the new tanks using the manual cleaning methods after each cleaning.

Please provide data that show how the [ ] tanks are qualified and the cleaning procedures are validated.

Your corrective action to replace [ ] tanks with [ ] is noted. However, it is your responsibility to ensure that equipment used to process heparin sodium does not meaningfully alter quality of the API by being additive, reactive or absorptive.

Once you have installed and qualified the [ ] please provide information on equipment qualification and cleaning validation for these tanks.

The inspectional observations listed on the FDA-483 and the concerns described above indicate significant deficiencies in your overall quality system. An effective quality system must assure that a firm's manufacturing operations are adequate and that the API meets its established specifications for identity, quality and purity. There should be a quality unit that is independent of production and capably discharges quality assurance and quality control responsibilities. Please respond to the FDA with your corrective action plan to address the above concerns with respect to your quality system.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMP that exist at a firm. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practice.

Shipments of articles manufactured by your firm are subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C Act [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. 351(a)(2)(B)]. Until all corrections have been completed and FDA can confirm compliance with CGMP, this office will continue to recommend disapproval of any new applications or supplements listing your firm as the manufacturer of active pharmaceutical ingredients.

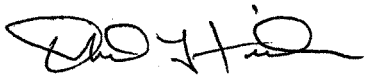
Please respond to this letter in English (including attachments) within 30 days of receipt and identify your response with FEI# 3003335664. Any future shipments of API manufactured at your 3 Changhong West Road site will be refused admission into the United States.

Please contact Anthony A. Charity, Compliance Officer, at the address and telephone numbers shown below, if you have any questions or concerns regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue, Bldg 51, Room 3246
Silver Spring, MD 20993
Tel: (301) 796-3191; FAX (301) 847-8741

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigation, HFC-134, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,



Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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Associated Press

**APFN FDA Budget Hearing; FDA chief walks careful line on agency's funding needs**

By MATTHEW PERRONE
AP Business Writer
508 words
15 April 2008
05:51 pm GMT
Associated Press Newswires (APHO)
English


WASHINGTON (AP) - The **head of the Food and Drug Administration says his agency simply could not handle the massive funding boost** that outside advisers say it desperately needs.

FDA Commissioner Andrew von Eschenbach appeared before Senate lawmakers Tuesday to discuss the agency's 2009 fiscal budget on the heels of a string of product safety problems that have battered the agency's reputation.

Over the past two years FDA has been at the center of deadly recalls involving everything from E. coli-tainted spinach to chemical-laced pet food and contaminated blood thinning drugs.

The Bush administration seeks a $54 million, or 2 percent, boost from the agency's 2008 fiscal budget of $2.3 billion. But FDA's panel of outside advisers recently said the agency needs $375 million next year to begin repairing its understaffed, outdated food and drug safety operations. The Senate recently passed a resolution supporting that increase.

Still, Eschenbach said the agency would be unable to absorb and allocate that much more money in a single year, noting the time-consuming process of recruiting and training hundreds of new employees.

Von Eschenbach walked a careful line during the hearing, stressing the need for increased funding but never characterizing the administration proposal as too small.

"I believe we need additional resources," von Eschenbach said. "I believe we would apply any additional resources wisely and effectively."

Democratic Sen. Herb Kohl, who chairs the subcommittee that oversees FDA's budget, questioned whether the administration's budget recommendation would increase the agency's staffing at all. He pointed out that FDA needs $60 million merely to maintain its existing employees.

"What this really suggests to me is that any additional money you claim to be for new food and medical safety activities will really be used to maintain current staff," said Kohl. "There is no new money for food safety, medical products safety, or anything else."

Kohl pressed von Eschenbach on whether FDA is underfunded, but the commissioner sidestepped the question, calling the agency "eminently successful" and "the gold standard of regulation in the world."

"But if we wish to maintain that record we must adapt to this rapidly changing world," von Eschenbach said. "As our portfolio of responsibilities expands, so must our resources."

One of FDA's most immediate challenges is monitoring safety of low-cost imports from China. U.S. regulators have recalled a slew of contaminated Chinese products in the last year: tooth paste, seafood and most recently, the blood thinner heparin.

The drug has been associated with dozens of deaths and hundreds of allergic reactions since Baxter International Inc. recalled nearly all its vials of the drug earlier this year.

Von Eschenbach highlighted FDA plans to open a new office in China next month. The agency conducted only 17 factory inspections in the country last year, despite the fact there are more than 700 drug firms there subject to FDA scrutiny.

The New York Times

National Desk; SECTA

**Panel's Bipartisan View: F.D.A. Is Underfinanced**

By GARDINER HARRIS
608 words
16 April 2008
The New York Times
Late Edition - Final
15
English


WASHINGTON -- The Food and Drug Administration needs far more money than the White House has proposed for next year, senators of both parties said Tuesday.

"To us, it's clear that they're seriously underfunded," Senator Herb Kohl, Democrat of Wisconsin, said after a hearing of the Appropriations subcommittee, headed by Mr. Kohl, that oversees the agency's spending.

The subcommittee's ranking minority member, Senator Robert F. Bennett, Republican of Utah, agreed with Mr. Kohl and tried at the hearing to get the food and drug commissioner, Dr. Andrew C. von Eschenbach, to say how much more the agency could use wisely.

If lawmakers decide that the White House "was wrong and you needed to add another $100 million, just to pull a number completely out of the air, could you handle that?" Mr. Bennett asked.

Dr. von Eschenbach said he would "welcome an opportunity to present a scenario of portfolio options" for levels of financing.

The Senate passed a budget resolution last month that would make the F.D.A.'s allocated budget -- that part of its spending that comes from taxpayer revenue, as opposed to user fees paid by drug and medical device manufacturers -- $375 million greater in 2009 than this year. That would be a 20 percent increase, and Dr. von Eschenbach said he did not believe that the agency could absorb so large an addition in one year.

A report last year by a panel of outside advisers to the agency said American lives were in danger because the F.D.A. did not have the money, the staff or the scientific expertise to protect them. And in a speech last month, Dr. von Eschenbach acknowledged that the F.D.A. "may fail in its mission to protect and promote the health of every American" and that "peril exists."

But he was far less pessimistic in his testimony on Tuesday.

"I believe we have been eminently successful up to this period of time," Dr. von Eschenbach said. "We are the world's gold standard.

"But if we want to continue that level of excellence," he added, "we must change."

The Bush administration has proposed increasing the agency's allocated budget next year by 3 percent, to some $1.8 billion, not enough to pay even for increased costs. Dr. von Eschenbach spoke Tuesday about plans to hire up to 700 new employees for the F.D.A. staff, but he acknowledged that the agency would not have the money to do any hiring next year if the president's budget was adopted without changes by Congress.

"We are on a trajectory to increased staff," he said. "We just have to push it off a little."

Dr. von Eschenbach said the agency planned to open three new offices this year in the Chinese cities of Beijing, Shanghai and Guangzhou. The combined staff there is to total 13 people, 5 of them to be hired locally.

Addressing the controversy over the blood thinner heparin, the commissioner said in his testimony that contamination in samples whose active ingredient had been imported from China was "apparently, we suspect, done by virtue of economic

fraud," to enhance profit. This was the first time anyone at the F.D.A. had confirmed that the agency suspected that the drug's contamination had been deliberate.

But after the hearing, Dr. von Eschenbach said that he "probably went too far" in his testimony and that the agency did not have proof that the contamination had occurred as a result of fraud.

PHOTO: Senator Robert F. Bennett

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washingtonpost.com

# U.S. and China Dispute Conclusions About Tainted Heparin



By Marc Kaufman
Washington Post Staff Writer
Monday, April 21, 2008; 4:11 PM

American and Chinese officials publicly disputed each other's conclusions today about what caused a deadly spike in severe reactions to the blood thinning drug heparin. Each side essentially said that the other was to blame.

Chinese officials today rejected the Food and Drug Administration's conclusion that a synthetic compound from China found in tainted supplies of the blood thinner heparin was the likely cause of the hundreds of injuries and deaths associated with the drug. Later, Janet Woodcock, director of the agency's Center for Drug Evaluation and Research, said that extensive research had convinced the agency that tainted heparin from China had indeed caused the reactions.

In addition, Woodcock said that the contaminated heparin had been found in 11 nations, and that at least 12 Chinese companies had some batches of the tainted drug ingredient.

In the Chinese government's first public statements on the controversy, Jin Shaohong, a top official with the Chinese National Institute for the Control of Pharmaceutical and Biological Products, said the compound -- oversulfated chondroitin -- could not be "the root cause" of the adverse reactions to heparin, as the FDA has suggested.

Speaking at the Chinese Embassy in Washington, Jin said some of the batches of heparin associated with severe allergic reactions and distributed by Baxter International did not have the synthetic chondroitin in them. He also said heparin with the contaminant has been found in more than 10 other nations, but none has reported a similar spike in harmful allergic reactions.

Jin said the Chinese government was conducting its own investigation of the heparin issue that would include a visit tomorrow to Baxter's New Jersey manufacturing plant. He said the allergic reactions could have been created by impurities introduced while the raw heparin from China was further refined by Scientific Protein Laboratories (SPL) of Wisconsin and then prepared for distribution in New Jersey.

Jin said he wanted to visit the Baxter plant and take back some samples of the company's heparin for "further in-depth analysis and investigation," because "when you see it, you believe it."

Baxter spokeswoman Erin Gardiner said that her company disagreed with the Chinese conclusions, and that the oversulfated chondroitin appeared to be the problem. She also said the Chinese were incorrect when they said some batches of heparin that caused severe reactions did not contain the chondroitin.

Representatives of more than 12 nations, including the Chinese, joined the FDA last week in a closed-door meeting on heparin. This morning, the FDA issued a warning letter to the Chinese supplier of heparin, Changzhou SPL Company Ltd., which is wholly owned by SPL.

"Equipment used to manufacture heparin sodium USP is unsuitable for its intended use," the FDA told the supplier. Agency inspectors, who visited the Chinese facility in late February, also found that the

company did not properly evaluate its own suppliers, who provide crude ingredients from pig intestines.

The Chinese plant has been supplying heparin for American patients since 2004. The FDA acknowledged last month that it never inspected the plant because it confused it with another facility with a similar name, and Chinese officials said they did not inspect it because it was listed as a plant producing chemicals rather than pharmaceuticals.

The sharp spike in allergic reactions to heparin from November through February has become emblematic of the large and growing number of prescription drugs and drug ingredients being imported from lightly-regulated nations such as China and India. It has also highlighted the question of whether the FDA has the resources and will to regulate foreign-made drugs with the same intensity that it does American-made products. Numerous members of Congress have called for greater oversight, and the FDA has announced that it will soon open its first office in China.

The complexity of the issue was apparent at the Chinese Embassy news conference. Jin said categorically "that the results of our recent investigation and other available evidence do not support the theory that the root cause" of adverse reactions to heparin has been the oversulfated chondroitin that the FDA identified as the likely culprit. He said Chinese officials are as eager to find what caused the problems as Americans.

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## FDA: Heparin supplier's Chinese factory 'unsuitable'

By Bruce Japsen

Tribune staff reporter

2:41 PM CDT, April 21, 2008

The U.S. Food and Drug Administration today said a Wisconsin company's Chinese plant used to make the blood thinner heparin's active ingredient was "unsuitable for its intended use" and was not in a position to detect impurities in the product now linked to hundreds of potentially deadly allergic reactions.

The FDA is probing the China-based supply chain, where the active ingredient in heparin made by Baxter International Inc. originates. Health officials suspect it may have been intentionally contaminated with an animal-like substance similar to heparin that was put into the product to increase certain suppliers' profits.

In a stern warning letter to the general manager of Scientific Protein Laboratories (SPL's) Changzhou China plant manager that was released today, the FDA said its inspection two months ago of the plant revealed "significant deviations" from U.S. good manufacturing practices. In addition, the FDA said the plant's processing steps used to manufacturing heparin's active ingredient provided "no assurance" any impurities could have been effectively removed.

The plant was inspected in February for the first time despite several years of manufacturing heparin's active ingredient. FDA officials said the plant's inspection did not occur earlier because of a paperwork glitch.

For its part, Scientific Protein said the warning letter does not reflect Changzhou SPL's "actual state of compliance." Neither the FDA nor SPL or Baxter has revealed an exact root cause of the allergic reactions.

But SPL said the contaminant was introduced earlier in a supply chain that stretches through farm villages to hog farms in rural China.

"The contaminant found in certain lots of finished heparin product was not introduced in the manufacturing processes at Changzhou SPL or SPL," Scientific Protein said in a statement. "Based upon testing of crude heparin materials and reports from other manufacturers around the world, it is now clear that the suspect contaminant was introduced earlier in the supply chain in China and was widespread throughout the unrelated Chinese supply chains of many companies."

The FDA has said there are now 62 reports of deaths of patients who experienced one or more allergic reactions and who were infused with heparin from Jan. 1, 2007, through the end of last month, the agency said.

Baxter, meanwhile, is standing by its estimate of four deaths associated with its heparin since the beginning of last year.

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# China and U.S. Clash Over Cause of Heparin Deaths (Update6)

By Justin Blum

April 21 (Bloomberg) -- U.S. and Chinese officials argued publicly whether a contaminant from China in Baxter International Inc.'s blood-thinner heparin caused allergic reactions and deaths.

China determined the contaminant isn't to blame, and its scientists intend to inspect Baxter's heparin factory in New Jersey, said Jin Shaohong, a Chinese regulator, at a news conference today in Washington. U.S. regulators concluded the contaminant can trigger the side effects, said Janet Woodcock, a Food and Drug Administration official, in a call with reporters hours later.

Some samples of Baxter's heparin, whose main ingredient was made from pig intestines and imported from China, were contaminated with the cheaper substance, over-sulfated chondroitin sulfate, Baxter and the FDA said last month. Eighty- one people given heparin died since January 2007 after suffering allergic reactions, up from 62 announced earlier this month, according to data released today by the FDA.

``The over-sulfated chondroitin cannot be the root cause,'' said Jin, deputy director general of China's National Institute for the Control of Pharmaceutical and Biological Products, during the news conference at the Chinese embassy.

Some other companies' versions of heparin sold overseas included the contaminant and didn't cause side effects, suggesting another ingredient in Baxter's heparin may be to blame for the allergic reactions and deaths, Jin said.

``If this is the root cause, it would be universal,'' Jin said in an interview, referring to the contaminant. ``Why only Baxter?''

## FDA's Response

Woodcock, head of the FDA's drug division, responded that ``this contaminant is capable of triggering these types of reactions.'' The FDA hopes to have additional discussions with the Chinese over the scientific differences, Woodcock said.

The contaminated heparin has been found in 11 countries, according to the FDA. People in Germany suffered similar reactions to those in the U.S., Woodcock said. The reactions may be linked to the use of large doses of heparin, a practice that is more common in the U.S. than in some other countries where contamination was found, she said.

Twelve companies in China handled tainted heparin, according to the FDA. The agency doesn't know where in the supply chain the contamination was introduced.

The tainted heparin was made as long ago as 2006, though it appears to have entered the market in 2007, Woodcock said.

## Baxter Disputes China

Deerfield, Illinois-based Baxter also disputes the Chinese conclusion. The

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contaminant is ``likely the cause'' of the increased number of side effects, said Norbert Riedel, Baxter's corporate vice president and chief scientific officer, in a statement. Lab tests show no unusual reactions to Baxter's uncontaminated batches of heparin, according to the company.

While the U.S. and China disagree, the countries are ``working in what I think is a productive way,'' said Health and Human Services Secretary Michael Leavitt in a briefing for reporters today.

Baxter, which sold about half the heparin in the U.S., announced a recall in January. Heparin's uses include preventing blood clots during dialysis and heart surgery.

Chondroitin sulfate is taken orally as a dietary supplement to treat joint pain. The over-sulfated version found in the heparin was chemically modified to act like heparin, according to the FDA. The contaminant isn't approved by the FDA for use in heparin.

Over-sulfated chondroitin sulfate is generated in laboratories for experimental purposes, according to the FDA. It is chemically altered to add additional sulfates.

Baxter has said the contamination appears to have happened before the product reached the company's supplier, Scientific Protein Laboratories.

Warning Letter

The FDA today issued a warning letter to the Scientific Protein plant in China, called Changzhou SPL, saying the company hadn't adequately responded to ``deficiencies'' identified during a February inspection by the agency.

The FDA's letter doesn't reflect the ``actual state of compliance'' with manufacturing standards, Scientific Protein said in a statement. The contaminant was introduced in China before the raw ingredient reached the Scientific Protein plant, according to the statement.

Scientific Protein, based in Waunakee, Wisconsin, is majority owned by American Capital Strategies Ltd.

U.S. Suspicions

U.S. regulators suspect heparin was intentionally contaminated to increase profit, FDA Commissioner Andrew von Eschenbach told lawmakers at an April 15 hearing. He later told reporters that the agency had no evidence the contamination was intentional.

The U.S. last week hosted a two-day meeting of international regulators to discuss heparin. About 10 countries, including China, were represented, according to the FDA.

Recalls or warnings about heparin also have been issued in Australia, Switzerland, Germany, Italy, Denmark and Japan.

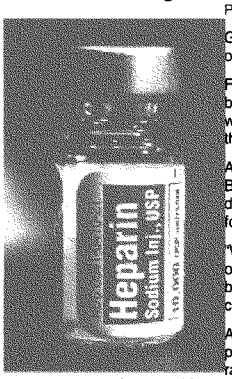
To contact the reporter on this story: Justin Blum in Washington at jblum4@bloomberg.net.

*Last Updated: April 21, 2008 19:01 EDT*

Wall Street Journal

## FDA Points Finger at China on Heparin Once More

Posted by Jacob Goldstein




Associated Press

Geopolitics, public health and global business all bubbled up in dueling press conferences over the heparin imbroglio today.

First, Chinese officials said the scores of deaths associated with the blood thinner may not be traceable to China after all. A few hours later, the FDA held its own press conference, where officials said they have evidence linking the deaths to a contaminant introduced into the drug during the manufacturing process in China.

Apparently, everyone agrees that batches of heparin were indeed contaminated in China. But the Chinese say patients have had adverse reactions associated with batches of the drug that weren't contaminated, suggesting that the Chinese contaminant isn't to blame for the health problems.

"We have tested this lot that they're referring to and have found contamination," an FDA official said this afternoon, when a reporter asked about the subject. "We are fairly certain because of multiple laboratories here doing the testing that this lot contains contaminants." (We described the contaminant in this post.)

Adding to the global confusion today, the FDA said separately that a factory in China that processed contaminated heparin hasn't put an adequate system in place to evaluate the raw ingredients that go into the drug.

Still, new screening techniques are in place in this country, and the threat to patients appears low at this point. The surge in adverse events related to the drug passed after Baxter pulled its contaminated heparin off the market in late February, and it shows no sign of returning.

REUTERS

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# US watchdog critical of FDA foreign drug oversight

Mon Apr 21, 2008 11:31pm EDT
(Adds FDA comment in paragraph 8)

By Lisa Richwine

WASHINGTON, April 21 (Reuters) - U.S. authorities increased inspections of foreign drug plants last year but still checked only a fraction of sites that supply medicine ingredients to the U.S. market, a government watchdog is set to tell Congress on Tuesday.

Concern about Food and Drug Administration oversight of foreign drug manufacturers has risen since the finding of a contaminant in some batches of blood-thinner heparin that were made with raw ingredients from China.

The Government Accountability Office will testify that the FDA increased inspections of foreign manufacturing sites to about 11 percent last year and took other steps in recent months, but made limited progress overall.

"FDA's plans represent a step forward in filling the large gaps in FDA's foreign drug inspection program, but do little to accomplish short-term change," said Marcia Crosse, health care director for the GAO, the investigative arm of Congress.

A copy of Crosse's testimony was provided to Reuters.

The FDA said on Monday it had determined the contaminant in heparin could trigger the types of sometimes-fatal allergic reactions reported in some patients treated with Baxter International Inc's (BAX.N: Quote, Profile, Research) brand of the product.

A House of Representatives subcommittee is set to question FDA Commissioner Andrew von Eschenbach about foreign drug inspections at a hearing on Tuesday where the GAO's Crosse and others also will appear.

FDA spokeswoman Julie Zawisza said officials "look forward to speaking with the committee about the challenges of globalization and potential solutions." The agency had no comment on the GAO testimony, she said.

More than 80 percent of active ingredients in U.S. drugs come from abroad, with more than half from India and China, lawmakers have said.

The GAO told Congress in 1998, and in November 2007, that the FDA was inspecting few foreign drugmakers.

The latest review found the agency checked 11 percent of more than 3,200 foreign ingredient makers registered with the FDA in fiscal 2007, which ended in September. Nineteen of more than 700 sites in China were among those inspections.

"FDA has made progress in conducting more foreign inspections, but it still inspects relatively few establishments," Crosse said.

The GAO estimated it would cost between $67 million and $71 million to inspect all 3,200 foreign sites every two years. The FDA has proposed spending about $11 million on foreign inspections in fiscal 2008, the GAO said.

"FDA will need to devote considerable resources to this area if it is to increase the rate of inspections. However, FDA's plans currently call for

incremental increases that will have little impact in the near future," Crosse said.

Congress is considering legislation meant to strengthen the FDA's oversight and increase funding for inspections.

"It's clear that FDA does not have the ability to protect the American people from unsafe food and drugs," House Energy and Commerce Committee Chairman John Dingell, a Michigan Democrat, said in a statement issued on Monday. (Editing by Braden Reddall and Mohammad Zargham)

The New York Times ROCK 'N ROLL WILL NEVER DIE

April 22, 2008

# U.S. Identifies Tainted Heparin in 11 Countries

By GARDINER HARRIS

WASHINGTON — A contaminated blood thinner from China has been found in drug supplies in 11 countries, and federal officials said Monday they had discovered a clear link between the contaminant and severe reactions now associated with 81 deaths in the United States.

But a Chinese official disputed the assertion that the contaminant found in the drug, heparin, caused any deaths and insisted that his country's inspectors be allowed to inspect the American plant where the finished heparin vials were made. He said any future agreement to allow American inspections of Chinese firms should be reciprocal.

"We don't have a strong evidence to show that it is heparin or its contaminant that caused the problem," said the official, Ning Chen, second secretary at the Chinese Embassy.

Mr. Chen said that illnesses associated with contaminated heparin had occurred only in the United States, which he said suggested that the problem arose in this country.

Dr. Janet Woodcock, director of the Food and Drug Administration's drug center, said that German regulators uncovered a cluster of illnesses among dialysis patients who took contaminated heparin. She said Chinese officials had conceded that heparin produced in their country contained a contaminant, though they say it was not connected to the illnesses.

"Heparin should not be contaminated, regardless of whether or not that contamination caused acute adverse events," Dr. Woodcock said. "We are fairly confident based on the biological information that we have had that this contaminant is capable of triggering these adverse reactions."

The dispute is a sign of growing tensions between China and the United States over the safety of Chinese imports. China has in recent years exported poisonous toothpaste, lead-painted toys, toxic pet food, tainted fish and now, contaminated medicine.

Bills to require far more aggressive inspections of Chinese products and companies are being proposed by members of Congress. Hearings are scheduled for Tuesday in the House and Thursday in the Senate.

China has lurched between defensiveness and cooperation on issues of product safety. Last year, it initially blocked the F.D.A. from investigating tainted pet food and accused foreign forces of exaggerating the issue. Then in July, China said that it had executed its former top food and drug regulator for taking bribes and promised reforms.

The F.D.A. sent a warning letter on Monday to Changzhou SPL, the Chinese plant identified as the source of contaminated heparin made by Baxter International in the United States. It warned that the plant used unclean

tanks to make heparin, that it accepted raw materials from an unacceptable vendor and that it had no adequate way to remove impurities.

Heparin is made from the mucous membranes of the intestines of slaughtered pigs that, in China, are often cooked in unregulated family workshops. The contaminant, identified as oversulfated chondroitin sulfate, a cheaper substance, slipped through the usual testing and was recognized only after more sophisticated tests were used.

The F.D.A. has identified 12 Chinese companies that have supplied contaminated heparin to 11 countries — Australia, Canada, China, Denmark, France, Germany, Italy, Japan, the Netherlands, New Zealand and the United States. Deborah Autor, director of compliance at the F.D.A.'s drug center, said the agency did not know the original source of all the contamination or the points in the supply chain at which it was added.

Officials have discovered heparin lots that included the cheap fake additive manufactured as early as early as 2006, although a spike in illnesses associated with contaminated heparin began in November and persisted through February, officials said.

Separately, the Government Accountability Office will release a report on Tuesday showing that the F.D.A. would need to spend at least $56 million more next year to begin full inspections of foreign plants. It would need to spend at least $15 million annually to inspect China's drug plants every two years, which is the domestic standard.

Bush administration officials have acknowledged problems associated with poor inspection of overseas plants and have plans to improve the situation. But President Bush's budget does not provide the F.D.A. with funds to hire more inspectors.

At its present inspection pace, the F.D.A. would need at least 27 years to inspect every foreign medical device plant that exports to the United States, 13 years to check every foreign drug plant and 1,900 years to examine every foreign food plant.

Proposals circulating on Capitol Hill would increase the agency's financing and charge domestic and foreign manufacturers fees to pay for inspections.

"Even the Bush administration seems to understand the potential peril that these foreign firms pose, but they offer only vague plans to address the problems and they refuse to spend more than a fraction of the money needed to protect the public," said Representative John D. Dingell, a Michigan Democrat who leads the House Committee on Energy and Commerce.

The F.D.A. has announced plans to open inspection offices in three Chinese cities, but the agency has yet to get permission from the Chinese government. Mr. Chen said any inspection agreement should be reciprocal. "Will the U.S. government accept the Chinese F.D.A. to set up in the United States?" he said.

Dr. Woodcock said the Chinese had agreed to test heparin lots before allowing them to be exported. But Dr. Moheb Nasr, director of the drug agency's office of new drug quality assessment, said that the Chinese test might not be sensitive enough to identify the contaminant.

Dr. Woodcock assured patients, however, that all heparin supplies in the United States had been tested with the most sensitive assays and had been found to be uncontaminated.

Scientific Protein Laboratories and Changzhou SPL said the company regretted the agency's decision to send a warning letter that, it said, did not reflect the company's current safety practices. The company said it had no way of detecting a contaminant present in heparin supplies throughout China.

Baxter International, which bought heparin ingredients from SPL and sold the finished drug in the United States, said that its tests confirmed that the contaminant could cause illness. It disputed the F.D.A.'s analysis that its product was linked with 81 deaths, saying it had identified only 5 in which its product "may have contributed to the adverse outcome, though there is not yet enough medical data available to draw a firm conclusion that the reaction caused the death."

Deaths linked to the drug may have been concentrated in the United States because American doctors may be more likely to use large, quickly infused amounts of the drug, said drug officials. Also, the F.D.A. may track serious side effects better than its counterparts abroad.