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EVALUATING THE EFFECTIVENESS OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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EVALUATING THE EFFECTIVENESS OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT

THURSDAY, MAY 3, 2001

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 2322, Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Upton, Greenwood, Deal, Burr, Whitfield, Ganske, Norwood, Bryant, Buyer, Brown, Waxman, Strickland, Barrett, Capps, Pallone, Deutsch, Eshoo, Stupak, Engel, Wynn, and Green.

Also present: Representatives Harman and McCarthy.

Staff present: Brent DelMonte, majority counsel; Marc Wheat, majority counsel; Kristi Gillis, legislative clerk; and John Ford, minority counsel.

Mr. BILIRAKIS. Let's get started, please. I am advised that we will have votes constantly today. Apparently there will be an awful lot of procedural votes called. I'll ask all the witnesses to forgive us in advance, but that is the way it is.

In the interests of time too, I would hope that the opening statements can be kept very brief so that we can do as much as possible before that first vote is called.

Today we are here to consider whether the Food and Drug Administration Modernization Act, which we fondly refer to as FDAMA, has revitalized the FDA for the benefit of patients, consumers, and industry. The purposes of the law were clear: Congress wanted the FDA and industry to work collaboratively in the consideration of applications for safe, effective drugs and devices. We wanted to ensure that food consumers would have access to legitimate health and nutrition content claims.

Clearly, however, no one advocated that the FDA sacrifice its safety and efficacy requirements to achieve these goals. To the contrary, our intent was to create a consistent process and enable all stakeholders to know precisely what is expected of them.

Today we will learn more about whether the hope represented in the FDA Modernization Act has been realized. Of particular interest to me is the pediatric exclusivity section of the act and the authorization for these provisions, the fact that the authorizations for these provisions expires this year.

Because so few drugs taken by children are labeled for pediatric uses, Congress created an incentive for drug makers to conduct tests which could increase pediatric labelling.

In exchange for conducting pediatric studies at the request of the FDA, drug makers received 6 months of additional patent exclusivity. The response to this provision has been overwhelmingly positive. The FDA has issued 188 written requests for the industry to conduct 411 pediatric studies. There have been 18 label changes for the benefit of children, with more to come.

This is not a partisan concern, I like to think. In fact, the Clinton Administration noted just this past January, "The pediatric exclusivity provision has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling."

While the pediatric research incentives have clearly worked well, some have argued for changes in the law. For example, to promote testing on drugs with no patent protection or exclusivity remaining. I believe that this is a legitimate problem which we should consider in our discussions of a reauthorization measure. At the same time, we must avoid changing the incentives in a way which results in fewer pediatric studies.

I am also interested in learning more about how FDAMA has worked to improve the availability of medical devices for patients. What is it, a vote?

Mr. PALLONE. Adjournment.

Mr. BILIRAKIS. Adjournment?

How would you handle that, Mr. Waxman?

Mr. WAXMAN. Keep going.

Mr. BILIRAKIS. Keep going. Under the law, FDA was directed to work with industry in creating a least burdensome standard to demonstrate the effectiveness of devices. On Tuesday, more than 3 years after the act's passage, this standard was finally issued. We need to understand why the FDA took so long to accomplish its task, whether the result will be beneficial for patients, and how the FDA plans to ensure that the standard is properly articulated to device reviewers.

I again want to thank all of our witnesses for taking their valuable time to join us and share their expertise. I know we all look forward to their testimony and their continued input and guidance as the subcommittee works to advance the reauthorization measure.

I will now recognize Mr. Pallone.

Mr. PALLONE. I was going to ask Mr. Waxman to go first.

Mr. BILIRAKIS. Mr. Waxman. I think I should always start with Mr. Waxman, because you all seem to want to yield to him, which is okay with me.

Mr. Waxman?

Mr. WAXMAN. Thank you very much, Mr. Chairman, and Mr. Pallone. There is a meeting of another subcommittee on the California energy problems, so I asked if I could go first in making my opening statement.

This is an issue I care a great deal about. At the end of this calendar year, the pediatric exclusivity authorities of the FDA expire. With my colleague from Pennsylvania, Mr. Greenwood, I was the

original author of this legislation. We proposed it because we were convinced that the regular drug development marketplace was not working in the best interests of children. At that time, 80 percent of all drugs on the market had not been tested for safety in children. Many of the most important drugs for childhood diseases had never been studied in children, and children were often left waiting years to be able to take advantage of research progress.

For almost 30 years, child health advocates, pediatricians, and the FDA had appealed to the pharmaceutical manufacturers for health, but nothing happened. The industry said nice things about child health, but they were uninterested in using their research powers and their financial clout to do anything real. So finally we developed a market incentive to pay manufacturers to do what many of us thought they should be doing as a matter of course. That is, produce results.

Pediatric research on some pharmaceuticals is happening now. I am pleased that industry has turned its attention to children's health. But it is still not clear to me that we are getting what we bargained for. Most obviously, it is not clear that the drugs that most need study are being studied. Many of the most important drugs for serious and life-threatening pediatric diseases are still not under review. Many of the drugs that are under review are not the most important ones for children.

Also, obviously we are often paying vastly more than we should for the research. Studies that cost hundreds of thousands of dollars are resulting in hundreds of millions in windfall profits. These windfalls total billions of dollars. These windfalls come out of Americans' pockets because of this legislation as surely as they would if we had increased taxes and paid billions for pediatric trials directly. One of five pharmaceutical dollars is paid directly through government programs. The rest by private insurance companies and by patients themselves.

Each time we extend patents or exclusivity, however laudable the purpose, we spend the public's money. I stand ready and willing to do whatever we must to improve pediatric research on pharmaceuticals. It is a good and important goal. I expect that we will ultimately reauthorize the pediatric exclusivity, but as we consider reauthorizing this legislation, I want to know if we are getting the research we need and if we are purchasing this research prudently.

Thank you very much, Mr. Chairman.

Mr. BILIRAKIS. I thank you, Mr. Waxman.

Dr. Norwood?

Mr. NORWOOD. Thank you very much, Mr. Chairman. I do appreciate this hearing very much. In consideration of the witnesses, I will simply ask you to put my opening statement in the record and move us on.

[The prepared statement of Hon. Charlie Norwood follows:]

PREPARED STATEMENT OF HON. CHARLIE NORWOOD, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Thank you Mr. Chairman. I thank you for calling this hearing, and applaud your efforts to further the review of the Food and Drug Administration Modernization Act. I am particularly interested in the pediatric exclusivity provision, included under Title I of the Act.

In January of last year, the FDA report on pediatric exclusivity reported that between the years of 1991-1996, prior to pediatric exclusivity, only 11 requests for studies were honored by the pharmaceutical industry. Since 1998, when the pediatric provision was implemented, the pharmaceutical industry has agreed to perform 411 drug studies. The report went further to suggest that the absence of appropriate labeling poses significant risks to the children of America; and, that the Secretary projected that the additional costs to the nation's pharmaceutical bill due to pediatric exclusivity amounts to only one-half of one percent.

While there are some out there that feel that the costs to sponsor study requests by the FDA are unacceptable, I am far from convinced those costs are unacceptably high where the health of our children is concerned. To make pediatric exclusivity contingent only on a positive label change will deter the pharmaceutical industry from further studies. If exclusivity is not to be granted, or revoked, based on a negative label change; then, what incentives have we presented the industry to further research?

I thank all of the witnesses for attending the hearing this morning and I look forward to hearing from each of the witnesses. Again, Mr. Chairman, I commend you for calling these hearings and leading the efforts to insure the safety of America's children, and I yield back the balance of my time.

Mr. BILIRAKIS. Mr. Pallone, an opening statement?

I thank the gentleman from Georgia.

Mr. PALLONE. Thank you, Mr. Chairman, for holding this hearing on the evaluation of the effectiveness of the FDA Modernization Act. There are several FDA issues that concern me, including the need to promote generic drugs as a method to hold down prescription drug prices, the lack of progress on dietary supplement regulations, and the current administration's inadequate attention to food safety.

I want to mention several things Congress can do to increase access to low-cost generic alternatives to name-brand products. The first is to stop a practice being used by some in the brand industry to prevent generics from reaching the consumer. These restrictive laws are being advanced despite a scientific finding by the FDA that the generic drug is equivalent and substitutable to the brand name product.

Congress needs to pass legislation prohibiting keeping generics off the market once the FDA has determined they are therapeutically equivalent to a brand name product. I have introduced legislation titled the Generic Drugs Access Act of 2001, which would accomplish just that. I hope, in light of the well-documented price discrimination that seniors face today, this committee would consider this legislation.

The second issue I wanted to mention concerns the lack of generic competition in the biotechnology industry. In my view, the lack of a clear regulatory framework for approving generic biotech products promises to become yet another obstacle blocking consumer access to lower cost alternatives. Indeed, the patents on a number of giant biotech products have already expired, and many more will expire in the next few years.

Mr. Chairman, there is no scientific reason why biologics should be exempt from the Hatch Waxman Act. Actually, I told Mr. Waxman I was going to say Waxman Hatch Act. We will save enormous sums of money if an explicit framework for approving generic biologics can be established through statutory language. Generic competition in the pharmaceutical industry has been an incentive for innovation at the same time it has lowered prices. I expect the

same would happen in the biotechnology industry if Waxman Hatch is expanded to include biologics.

Mr. Chairman, I am also concerned about the manner in which the FDA is implementing the pediatric exclusivity provisions of FDAMA. The intent of the law was to create an incentive for companies to discover new uses in pediatrics for their products in exchange for 6 months of exclusivity for the work done. The FDA's interpretation of the law, however, has in essence been granting companies patent extensions without receiving the pediatric benefits it was intended to generate.

Two areas I am particularly concerned about are the ability of companies to use old studies to obtain patent extensions and the granting of exclusivity based on active moiety rather than on product-by-product basis. The pediatric exclusivity provision of FDAMA should be prospective, and needs to be strengthened.

Mr. Chairman, the issue of dietary supplement regulations is not progressing, in my opinion, in a timely manner. The industry and the public have been asking for the proposed final regulations for good manufacturing practices and the publication is still pending at the FDA. The discussion today examines modernization of the FDA, yet it takes more than 6 years to get quality standard regulations for dietary supplements.

In addition, we are awaiting publication of the Department of Health and Human Services Inspector General's report seeking tighter regulations on dietary supplements. The final draft of the report allegedly requires mandatory reporting of supplements and their ingredients. Not only does the draft report unfairly paint a biased picture of the industry, it also understates the benefits of supplements.

Last, Mr. Chairman, the country is facing a crisis in food safety. The FDA is in need of food safety modernization in terms of better inspections and better labeling. I am introducing two bills to address these issues, but I want to highlight the fact that the Bush Administration's food safety record in its first 100 days is dismal. I am interested in hearing from Dr. Applebaum of the National Food Processors Association on this urgent issue.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman. I will advise the gentleman that I have talked to the committee staff over the last few days. We are going to devote an entire hearing to the generic drug issue.

Mr. PALLONE. Thank you, Mr. Chairman.

Mr. BILIRAKIS. I think in order for all of us to be able to make this very important vote, I am going to have to break, unfortunately. So forgive us. I'll run right on back. As soon as I get back, we'll get started.

[Brief recess.]

Mr. BILIRAKIS. Mr. Whitfield, for an opening statement?

Mr. WHITFIELD. Mr. Chairman, thank you very much. I've been looking forward to this hearing today. I commend you for initiating the holding of this hearing.

I would initially, Mr. Chairman, with unanimous consent ask that I submit for the record a copy of a statement of the Grocery Manufacturers of America. This is an issue of particular impor-

tance to them. Even though they are not testifying, they would simply like to get their views reflected in the record.

Mr. BILIRAKIS. By all means, without objection, that will be the case.

[The statement follows:]

PREPARED STATEMENT OF GROCERY MANUFACTURERS OF AMERICA

GMA is the world's largest association of food, beverage, and consumer brand companies. GMA member companies sell more than $460 billion in consumer food and other products each year and employ more than 2.5 million workers in all fifty states. GMA speaks for food and consumer brand manufacturers at the state, federal, and international levels on legislative and regulatory issues.

GMA and its members were deeply involved in the consideration and enactment of both the Nutrition Labeling and Education Act (NLEA) of 1990 and the Food and Drug Administration Modernization Act (FDAMA) of 1997. We have appeared at FDA hearings to discuss implementation of these two statutes and have submitted comments to the agency on proposed regulations intended to implement them. We welcome this opportunity to present our views on these important matters to the Subcommittee at this time.

GMA's comments will cover five different areas: (1) FDA's highly restrictive regulation of disease/health claims under the NLEA of 1990 and the FDAMA of 1997, (2) the failure of FDA to implement the January 1999 decision of the United States Court of Appeals in the *Pearson* case, that applied the free speech provisions of the First Amendment to food labeling, (3) the expansive regulation by FDA of structure/function claims as implied drug claims rather than as food claims, (4) the successful implementation by FDA of the new approach to regulation of indirect food additives under FDAMA, and (5) the continuing need for national uniformity in all aspects of food regulation.

1. FDA's Highly Restrictive Regulation of Disease/Health Claims for Food.

Initially in the NLEA of 1990, and subsequently in the FDAMA of 1997, Congress sought to expand the availability in food labeling of helpful information for consumers about the relationship between diet and disease. By its narrow and constricted implementation of these provisions, however, current FDA policy prevents important health information from reaching the American public. This is detrimental to both personal and public health. There are five ways in which FDA has failed to implement NLEA and FDAMA in the way intended by Congress.

First, NLEA requires FDA to approve any claim relating to the relationship between a nutrient and disease if it is truthful, nonmisleading, and is supported by significant scientific agreement. On its face, this statutory provision authorizes claims about a diet/disease relationship based upon preliminary research or emerging science, where the evidence is not yet definitive, as long as the state of scientific development is accurately described. Nonetheless, FDA has chosen to interpret and apply this provision only where there is overwhelming science to support a diet/disease relationship, thus preventing the public from learning about new scientific developments until they have matured into hard science. This was not the intent of Congress and it is not in the public interest.

GMA strongly believes that this provision of the law is being improperly implemented and that the FDA approach prevents consumers from obtaining important health information. We urge the new Administration to reverse the FDA approach and to implement the law as it was written.

Second, FDA has interpreted the statutory standard of "significant scientific agreement" so narrowly and stringently that very few diet/disease relationships can stand up to the FDA requirements. As a result, FDA has approved only a handful of disease/health claims under the NLEA and the FDAMA, in spite of strong scientific evidence supporting a number of other diet/disease relationships. As a practical matter, the FDA interpretation of this provision approximates the requirement of a full scientific consensus. This was never the intent of Congress.

GMA urges the new Administration to return the standard of "significant scientific agreement" to its original intent. A reasonable scientific basis, rather than overwhelming scientific proof, should be sufficient to support claims as long as the basis for those claims is adequately characterized.

Third, FDA has insisted upon "model" disease claims that are lengthy, detailed, and complex, and thus poorly suited for consumer understanding and communication. The food industry has decades of knowledge and experience in consumer communication. FDA has little or no expertise in this area. FDA should approve the

basic diet/disease relationship and allow the industry to determine how best to communicate that relationship to the consuming public, as long as the claims remain truthful, accurate, and nonmisleading.

Fourth, FDA has narrowed the statute to permit only disease prevention claims and to exclude disease treatment claims. Nothing in the statute authorizes such a limitation.

It is readily apparent that food can treat as well as prevent disease. Numerous foods are used as part of a therapeutic regimen. People with some types of heart disease or hypertension are placed on strict diets designed to treat their existing condition. There is no statutory or public health basis for the FDA limitation on disease/health claims and as a result, people who should be told about the dietary means of treating disease are denied this important information.

Fifth, frustrated with FDA's continuing restrictions on disease/health claims in food labeling, in 1997 Congress included in FDAMA a specific provision to expand disease/ health claims by authorizing their use based upon authoritative statements by other federal science agencies and the National Academy of Sciences. Once again, however, FDA has severely blunted the intent of Congress by interpreting this provision to allow FDA to veto any claim authorized by another agency if FDA disagrees with that other agency. This policy has effectively eviscerated the FDAMA provision.

GMA urges the new Administration to adhere to the intent of Congress and to respect the published position of the federal science agencies as Congress intended.

2. FDA's Failure to Implement the Pearson Decision

In the landmark case of *Pearson* v. *Shalala,* 164 F.3d 650 (D.C. Cir 1999), the United States Court of Appeals determined that the restrictive implementation by FDA of disease/health claims for food labeling under the NLEA represents an unconstitutional limitation on free speech. FDA was ordered by the court to approve disease/health claims in food labeling that, when considered with accompanying explanatory information or disclaimers, are accurate, truthful, and not misleading.

This particular court case arose in the context of four claims that had been petitioned for use in connection with dietary supplement products. As a result, FDA has limited the *Pearson* decision to dietary supplement claims and has refused to apply the same principles to conventional food claims.

There is no basis either in the NLEA or in the Constitution itself for distinguishing between disease/health claims in dietary supplements and in conventional food. If a disease claim is supported for one, it is supported for the other (absent some clear scientific basis for a distinction).

GMA initially petitioned FDA to abandon its policy on this matter. In response, FDA wrote a member of Congress saying that it would not apply the *Pearson* decision unless and until ordered by a court. GMA has therefore petitioned FDA explicitly to adopt the same claims for conventional food that it has now approved for dietary supplements under the *Pearson* decision. If FDA fails to respond, or denies this petition, GMA is prepared to resort to the courts in order to preserve the First Amendment rights of those firms that manufacture and market conventional foods.

We would very much prefer not to have to go to court to settle this matter. GMA urges the new Administration to reverse the current FDA policy and to recognize that *Pearson* applies to conventional food, and indeed to all products regulated by FDA.

3. FDA's Expansive Regulation of Structure/Function Claims As Implied Drug Claims.

Since 1938, the Federal Food, Drug, and Cosmetic Act has recognized that claims relating to the effect of food on the structure or function of the human body may appropriately be made in food labeling without the product being classified as a drug. Under the Dietary Supplement Health and Education Act of 1994, structure/ function claims are explicitly permitted for dietary supplement products as a "safe harbor" from drug regulation. In establishing regulations to distinguish between structure/function claims that are permitted for food (including dietary supplements), and disease/health claims that are only permitted for drugs, FDA has announced a policy that many structure/function claims would be regarded as *implied* disease claims and therefore would not be permitted for food. Once again, this exceeded the intent of Congress.

It is clear that any claim relating to the effect of a food or nutrient on the structure or function of the human body will inherently imply some utility for the prevention or treatment of disease. It would be virtually impossible to formulate a structure/function claim that did not have this potential implication, whether directly or indirectly. Thus, FDA has denied to the food industry, by its new regula-

tions, numerous important structure/function claims that provide important health information to consumers.

For example, FDA states that an appropriate structure/function claim is limited to "helps maintain healthy cholesterol levels" and does not include "helps reduce cholesterol levels to a healthy level." This policy cannot possibly be defended on public health grounds.

GMA urges the new Administration to reverse this policy. Structure/function claims that only indirectly imply utility in preventing or treating disease should be regarded as appropriate for food products in order to educate the public about important health aspects of the daily diet.

FDA's Successful Implementation of the new Indirect Food Additive Provisions.

Under FDAMA, Congress authorized a new approach of premarket notification for the regulation of indirect food additives, i.e., food additives that are used in packaging food or for other food-contact purposes but that are not directly added to food. This provision has been implemented by FDA in a direct, efficient, and effective way. FDA is to be commended on formulating and following a policy that has replaced an inefficient and ineffective premarket approval approach with the new streamlined premarket notification system. GMA believes that this model could appropriately be used in other areas of food regulation as well, as a substitute for lengthy, costly, and ultimately unworkable premarket approval.

5. The Continuing Need for National Uniformity in Food Regulation.

The NLEA advanced toward the important goal of national uniformity in food regulation. NLEA provided national uniformity for most aspects of food labeling. It failed, however, to include national uniformity for food warnings or for food safety. GMA believes that, in order to have a comprehensive and integrated national system of food protection, enactment of national uniformity legislation is essential.

Our nation-wide economy cannot support fifty differing state laws and regulations governing the food supply. Interstate commerce throughout the wide reaches of our country requires a consistent, uniform, and predictable system of laws and regulations that permit transport of food under a single set of regulatory standards. GMA has actively sought both administrative and statutory adoption of national uniformity in food labeling for the past several years, and will continue to seek this objective until it is ultimately achieved.

Mr. WHITFIELD. In addition to that, Mr. Chairman, I would just simply say that the aspects of this hearing today, we cover a number of different areas. Labelling is one of those areas that I was quite involved in when we passed this legislation back in 1996 or 1997. While generally I have been pleased with the progress that has been made in that area, I do think that there has been some real disappointment in the way that FDA has proceeded on this particular aspect of it.

Rather than getting into it with my statement, I will be asking some questions as we go through the hearing. With that, I yield back the balance of my time.

Mr. BILIRAKIS. I appreciate that. It looks like we may be going into recess where they are going to try to get things worked out. So we may have a little bit of relief here.

Without objection too, the opening statements of all members of the subcommittee will be made a part of the record. The Chair now recognizes Mr. Brown, the ranking member.

Mr. BROWN. Rationality is winning out on the House floor.

Thank you, Mr. Chairman. I would like to thank Dr. Suydam and other distinguished witnesses for joining us this morning. The title of this hearing is evaluating the effectiveness of the Food and Drug Administration Modernization Act.

If you consider the major goals behind the legislation, that enactment, you have to say that FDAMA has been quite effective. With the exception of the pediatric provisions, the overriding purpose of FDAMA was to streamline the approval of drugs and devices, and

relax what the food industry perceived as overly stringent restrictions on health and nutrient claims.

Are new drugs and devices approved more rapidly now? Absolutely. Are drug manufacturers conducting more pediatric clinical trials? Absolutely. Are the health claims and other food-related provision in FDAMA the right ones to meet the concerns of the food industry? Based on their written testimony, the National Food Processors Association still feels the FDAMA provisions are on target. It's the implementation of those provisions that needs some fine-tuning.

If effectiveness is your standard, FDAMA is a success. My concerns regarding FDAMA do not have to do with effectiveness. They have to do with cost effectiveness.

As we work on reauthorizing the pediatric exclusivity provisions of FDAMA this year and the PDUFA provisions of FDAMA next year, we need to look both at the benefits and the costs of the new FDA. The maintenance of effort provisions in FDAMA require FDA to spend up to pre-specified levels on new drug approvals before user fees kick in. The authorized spending threshold stands regardless of FDA's annual appropriation.

As a result, FDA has been forced to channel very finite resources from other FDA functions into new drug approvals. That means several things. There are huge costs associated with starving other FDA activities, like generic drug approvals, like market surveillance, like food safety initiatives to accommodate new drug approvals.

It takes 12 months on average to review a new drug application or NDA, as we call it. Six months, if it's a so-called fast-track drug. It takes 18 months on average, however, to approve a generic drug application, a so-called ANDA.

There are about 300 scientists on staff to review generic drug applications. There are 2,100 scientists on staff to review: 300 for generic applications, while 2,100 on staff to review new drug applications. Delayed access to generic drugs costs taxpayers literally billions of dollars each year.

To get a sense of these costs, the excess consumer spending associated with the pediatric exclusivity provisions are informative. HHS estimated that delayed access to the limited number of generics held up by the pediatric exclusivity provisions costs consumers and the Federal Government close to $700 million each year. Seven hundred million dollars per year for a 6 month delay in access to a handful of generics.

If you inflate that number to account for the fact that every generic drug currently faces an average 6 month delay in approval, it's clear that it's starving, as we really are doing, the Office of Generic Drugs. It's costing consumers billions of dollars a year in lost savings.

Let's consider the costs of under-funding food safety initiatives. Five thousand Americans it's believed die each year from food-borne illnesses. Hundreds of thousands of Americans are hospitalized each year from food-borne illnesses. Millions of Americans otherwise become ill from food.

In addition to the well-known and well-documented cases of food-borne illness, Americans need to be concerned about the emergence

of antibiotic resistant bacteria in food, genetically modified organisms of unknown risk, and lethal contaminants such as mad cow disease and others for which no detection test is currently available.

Yet we inspect—again, look at how this agency is starved when we shift resources—we inspect only seven-tenths of 1 percent of food imports. If anything, the enactment of FDAMA has intensified the need for post-market surveillance. Yet enactment of that legislation limits the resource available for that activity. We speed up the approval process. We spend more money on approval. We spend less money on post-market surveillance as drugs get in the marketplace more quickly. We spend more money—drug companies spend more money advertising those drugs. The use of those drugs begins much more quickly than it did in the past.

Because of FDAMA, there is immense pressure on FDA to approve new drugs and devices as quickly as possible. That, as I said, coupled with aggressive direct to consumer advertising, means that more people are exposed to new products more quickly. If something is wrong with one of these products, more lives are affected. We absolutely need to improve post-market surveillance of these new drugs and new devices. That requires resources.

None of these concerns means that we're spending too much on new drug approval. Not at all. It means we are spending too much on new drug approval relative to other priorities. We either need to increase spending on these other priorities or rethink the maintenance of effort requirements in FDAMA.

As we evaluate the cost-effectiveness of FDAMA, one of the most difficult calculations relates to the pediatric exclusivity provisions of the act. Pediatric testing and labelling are invaluable. The question is not whether the Federal Government should encourage, some would argue require drug companies to do this type of testing. The question is are we paying more than is necessary for pediatric testing.

Let's go back to the HHS estimates. The exclusivity provisions cost American consumers $65 million per drug. While the drug industry won't disclose the kind of information we need to estimate the cost of pediatric clinical trials, drug makers have to disclose information on the costs of orphan drugs, clinical trials to receive their tax credit. Based on that information, it costs about $3 million on average to conduct a clinical trial.

Still, just for argument's sake, take the industry's estimates for the cost of pediatric testing. They stated a cost from $5 to $35 million for a clinical trial. If we split the difference, we could hand the drug industry a check for twice their investment and still save money on pediatric testing relative to the exclusivity provisions. Even if you don't split the difference and assume that each and every clinical trial costs $35 million, and that's probably not true, we could promise the drug industry a 50 to 75 percent return on their investment and still save money. Even the most profitable industry in the world, which coincidently is the prescription drug industry, doesn't enjoy returns like that today.

The drug industry is fiercely protective of the pediatric exclusivity provisions. Hard to blame them. The Federal Government should be fiercely protective of the Nation's children. We should

make sure that prescription drugs are thoroughly tested and correctly labeled for pediatric use. That doesn't mean we should actively contribute to grossly inflated drug prices. That is simply not necessary.

I thank the Chairman, and look forward to hearing from the witnesses.

Mr. BILIRAKIS. Mr. Greenwood, for an opening statement.

Mr. GREENWOOD. Thank you, Mr. Chairman. I also thank you for holding these hearings.

I remember, Mr. Chairman, probably 6 years ago when then Chairman Bliley called me up and asked if I would chair a task force to reform FDA. I remember saying at the time that what I knew about FDA I could squeeze onto a three-by-five card, but I would be happy to do it. We put together a group. Mr. Burr headed up the pharmaceutical piece, Mr. Barton the medical device piece, Mr. Klug, former Member Klug, the food safety piece, and we engaged in a process that was agonizingly long and complex, where we interfaced with the industries, interfaced with the patient groups. We interfaced with the agencies. Spent days at a time with Dr. Kessler in my office, worked in I think a bipartisan fashion. It was difficult. It was controversial, but unlike a lot of effort that occurs around here, it produced a result of which I think we all can be proud.

By every measurement that I have been able to take since then, this is an act that has been successful. The fundamental problem that we were faced with is that the Food and Drug Administration understood that its role was to make sure that we maintained the gold standard in this country, that nothing, no drug, no device, no food product passed muster unless it was proved to be safe. The problem was that they didn't seem to have as a mandate the notion that they needed to nonetheless get these products to the patients expeditiously, and that someone was just as harmed and just as dead if they died waiting for a promising drug as they were if they took a drug that wasn't safe. I think that has changed. I think it has all been to the good.

I think the pediatric exclusivity, as I think we'll hear today in testimony, has been an extraordinary success. It solved the problem that was unresolved for decades. We have learned in the interim. We can refine this statute. I think all of the issues that members on both sides of the aisle have raised ought to be on the table. But I think we ought to be prudent because we don't want to go backwards. I think our first order of business should be to do no harm, and make sure that nothing that we do in any way undermines any of the success that we have had.

I think we ought to also make sure that we don't stall out on this behavior on this process over controversies. There is a very long list of very controversial areas we can get into that will probably be unresolvable, and could have the effect of causing us to fail to get these statutes reauthorized.

I look forward to working with members on both sides of the aisle, and am pretty confident that we can get that done. I yield back the balance of my time.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Deutsch, for an opening statement?

Mr. DEUTSCH. Thank you, Mr. Chairman. I would like to thank the chairman and the ranking member for calling this hearing.

Obviously the issues that we will hear about today are of great importance. All of our constituents rely heavily upon the drugs and medical devices that the FDA regulates. My district, as many of you know, is comprised of a large number of senior citizens. My constituents and actually obviously constituents throughout the country have been able to live longer and healthier lives because of the advances in pharmaceutical and medical devices in the last few years. Seniors can now take drugs that lower cholesterol and high blood pressure as well as take advantage of amazing medical devices such as stents to treat artery blockages.

I am going to mention just a couple of statistics and facts that I brought out. We just came back from a break period, had about 25 town meetings during that period, a number of them in senior communities. One of the things that is just a striking statistic to talk about what the FDA has been part of in the last 36 years since Medicare was created.

When Medicare was created in 1965, the average life expectancy of an American was 65 years old. That's an incredible statistic because today that life expectancy in the 36 years has increased by more than 10 years.

On the other side of this sort of statistics which I think sometimes statistics can in fact give us real insights, in 1965 before Medicare was created, the average out-of-pocket expenses for seniors for health care was 11 percent. Thirty-six years later, with Medicare paying most hospitalization and most physician fees as well as other fees, the average percentage of a senior in America's out-of-pocket costs for health care is now close to 19 percent of their income with Medicare existing.

I think those two statistics in many ways talk about the medical science and what has happened in the last 36 years. It is a different world. That is why so many people on this panel have been committed to providing prescription drug coverage as a benefit of Medicare. But it also is literally there are tens of millions of people who are alive today because of advances in medical science. So there is probably nothing more important, if you look at it in this global way, that the government has done than exactly what the FDA has done within its jurisdiction.

I think it is imperative that we take a look at reauthorizing FDAMA and PDUFA and we ensure that there is a proper balance between safety, economics, and timeliness. The FDA obviously has an important job in making sure that our constituents, have access to safe and effective products in a timely manner. I hope that we can hear from our witnesses today about how the current process functions and what, if anything, we can do to improve that.

I yield back the balance of my time.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Buyer, for an opening statement?

Mr. BUYER. Thank you, Mr. Chairman. I appreciate you holding the hearing and providing us to focus on the attention of the progress of the FDA Modernization Act of 1997.

As I understand it, one of the goals of the act was to shorten the review times of the FDA for new drugs and medical devices. As

we're all aware, patient health is not protected if they are denied the access to medical treatment due to the bureaucratic delay.

I am looking forward to hearing the testimony from the FDA and drug and device industries on the success in meeting the goals. One out of eight jobs in Indiana is in the health care industry. Medical technology is a significant and growing part of Indiana's economy, and it is important that government not impede the breakthroughs in pharmaceutical and medical technology that can improve the quality of life, not only of Hoosiers, but citizens in our country and around the world.

The United States is the global leader in the health care field. We certainly do not want to see our cutting-edge forfeited to overseas competition. To maintain the edge, government must be a partner in the approval process without sacrificing safety and efficacy. I know this is not an easy thing to do. I look forward to the hearing.

I yield back the balance of my time.

Mr. BILIRAKIS. I thank the gentleman.

Ms. Capps?

Ms. CAPPS. Thank you. Thank you, Mr. Chairman, for holding this hearing. It is a very important topic for our committee to entertain and discuss and the Congress as a whole to review its past actions from time-to-time. This is an appropriate way to spend our time, to measure our success and determine the need for future action.

I am particularly pleased that today we are focusing on the Food and Drug Agency Modernization Act and its implementation. The FDA is vitally important to the health and safety of the American people. Its review of new and existing drugs, devices, and food is an essential protection for our constituents. But it is also extremely important that efforts to protect people do not inadvertently cause them harm because they cannot get access to state-of-the-art care.

The state of medicine is dramatically changing every day. New technologies are being developed rapidly, and old technologies are in constant need of upgrades. There are always new ideas right around the corner, which is wonderful and one of the best things about our country. It means that many patients will be able to try out new treatments and improve their care. Many who have lost hope may have it restored. Others will see their quality of life improved by these new treatments.

But it creates a two-sided challenge, I believe, for the FDA. On the one hand, all the new technologies and ideas need to be vetted so that doctors, patients, and everyone else can have confidence that there is no unnecessary risk. New ideas mean much more work for the FDA. On the other hand, we have to make sure that we don't discourage innovation and that we make it easier for patients to get the benefits that have been discovered in a timely fashion.

If a new technology becomes bogged down in a review and is slow to help our constituents, then we have not achieved the potential of these innovations. It's a fine line to walk. We need to help you, we need to help the Food and Drug Administration to find the right path.

FDAMA was an excellent start. I want to applaud the FDA for the tremendous progress that it has made on this issue. But there are components of FDAMA which we need to review. It has already been mentioned, but I also believe that the development of pediatric exclusivity is one such change. Its implementation has meant that more and more drugs are being evaluated for use on children. This has meant a higher quality of care for our Nation's young people. But it has come at such a high cost, I mean literally. The extension of exclusivity has slowed the development of generic drugs and meant higher costs for consumers for a longer period of time. This may be a cost that we have to bear in order to improve children's health care. But we need to examine all of our options and really question whether we in this case do in fact have the right balance.

There may be a way to give companies an incentive to conduct these studies and still bring down the cost of prescription drugs. It is our responsibility to find this way or these ways if they do in fact exist. It means working together. I look forward to that opportunity to work with you to build on the changes that you have already introduced in FDAMA. More will always need to be done. So I conclude by saying that we can't afford to rest on our laurels. I know you don't want to either. We must continue to examine ways to improve the Food and Drug Administration and its processes. Thank you.

Mr. BILIRAKIS. I thank the gentlelady.

Mr. Burr, for an opening statement.

Mr. BURR. Thank you, Mr. Chairman, for holding this hearing. Let me thank all the witnesses who have volunteered to come.

When we were asked to start on FDAMA in 1995, there were many people within this institution that said this is a big thing, don't do it. Washington and Congress don't do things this big. It's because of the bipartisan approach that was taken, the partnership that was established not only across the aisle, but from Washington, from the Capitol and downtown, but more importantly, from the Capitol and across the country. As I read some of the testimonies, I am amazed to see the revisions of history as it relates to the process not including the American people.

Years were spent with patients groups, making sure that every anticipated result of FDAMA had a positive impact on people who were sick and dying. The only way that you could ever get legislation of this magnitude through this institution was for members to concentrate on patient health, to concentrate on a vision of the future, to concentrate on what it takes to unleash the capital that's needed privately and publicly for research and development, for better understanding of drug treatment and drug interactions.

We were able to find that balance. I will agree with some of my colleagues, it's not perfect. Don't judge Congress on whether we get it perfect or not. Judge us on whether we fix it, because we learn as the years go on. We are at a point that we have learned.

We have learned that through pediatric exclusivity, that companies are now going through the clinical process of some very valuable data that pediatricians across this country need to treat kids. I don't think anybody wants to take that away. Is the right length of exclusivity 6 months, 4 months or 12 months? We don't know,

but hopefully before we take the legislation up, we'll turn to experts that are in the field, not just in the pharmaceutical field. We'll turn to generics, but more importantly, we'll turn to pediatricians, the ones that actually treat our children, and ask them how does it work? What do we need to do? How long should the reauthorization be for?

Let me suggest to you that FDAMA was done for one reason and one reason only. It was to open the line of communication between companies and the approving agency. It was to make sure that there was no lack of communication because there was no desire to approve.

We spent 2½ years for one reason, because it was very difficult to protect the gold standard that was established at FDA, that we felt that was so important that anything that we did could not lower that standard. We had our critics, I will assure you. We met with every one of them. I think in the end, we got as close to maintaining that gold standard as any legislative process could do.

I would encourage our witnesses today to be honest. I would encourage my colleagues to be inquisitive. I would encourage the chairman to move quickly. Let's make sure that we reauthorize pediatric exclusivity. If we can this year, and it's the will of my colleagues, I hope we reauthorize PDUFA this year, not next year when it's up. Let's do it this year while there is political will and not an election that's looming.

To do big things in health care requires one to set aside politics and concentrate on patients. I am convinced, Mr. Chairman, that the atmosphere is such on both sides of the aisle that we're focused on patients. Let's move as quickly and as inclusively as we can toward the reauthorization.

I thank the chairman. I yield back.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Stupak?

Mr. STUPAK. I'll waive my opening statement, Mr. Chairman.

Mr. BILIRAKIS. The Chair appreciates that.

Mr. Bryant?

Mr. BRYANT. Thank you, Mr. Chairman. I also will waive my opening statement.

Mr. BILIRAKIS. I thank you.

Dr. Ganske?

Mr. GANSKE. I think it's time to move on, Mr. Chairman. I'll waive mine.

Mr. BILIRAKIS. Thank you, Dr. Ganske.

I will note that a gentlelady who is a member of the full Committee of Energy and Commerce but not a member of the subcommittee has asked to introduce a panelist from the next panel.

Please proceed.

Ms. MCCARTHY. I thank you, Mr. Chairman, for that courtesy. I thank the first panel for indulging me in this moment. But because of the importance of what this subcommittee is doing and the importance of what the full committee will eventually take up, I wanted the opportunity to introduce Dr. Greg Kearns to you.

Although the veterans on this committee will recall his testimony before the full Energy and Commerce Committee when we were initially approving FDAMA, he has now had the experience as a

champion of pediatric health care in my region at Children's Mercy Hospital, and certainly in the Nation, to come before you today and to reflect on how it's working and what further reforms might be needed, and certainly for the need to reauthorize pediatric exclusivity in the law.

He is a doctor of pharmacology and a professor of pediatrics and pharmacology at the University of Missouri, Kansas City. He is also the chief of the Division of Pediatric Pharmacology and Medical Toxicology and the program director of Pediatric Pharmacology Research Unit at Children's Mercy, and the clinics.

It's to me a very great effort that this subcommittee is making to take this up ahead of time and to try to reauthorize it because from everything that I have read in the testimonies that I have looked at, it is working for the benefit of our children. Dr. Greg Kearns is here today to reflect with you on how to it improve for the future.

Thank you very much, Mr. Chairman, for allowing me this opportunity.

Mr. BILIRAKIS. By all means, you are welcome.

[Additional statements submitted for the record follow:]

PREPARED STATEMENT OF HON. W.J. "BILLY" TAUZIN, CHAIRMAN, COMMITTEE ON ENERGY & COMMERCE

Mr. Chairman, I commend you for holding this timely hearing which will consider whether the reforms contained within FDAMA have successfully lessened regulatory burdens at the FDA.

FDAMA represents the first comprehensive re-write of our nation's food and drug laws in more than thirty years. It contains provisions intended to speed the approval of safe and effective drugs and devices, and provisions which help provide consumers with more health information about the food they eat. Today we are here to determine whether or not these reforms are working.

While all of the provisions contained within FDAMA are very important, a good portion of this hearing will focus on the drug title of the bill. This makes sense, as the pediatric exclusivity provision within FDAMA is up for reauthorization this year, and the Prescription Drug User Fee Act must be reauthorized before the end of next year. Allow me to explain the importance of these provisions.

According to the American Academy of Pediatrics, which will testify today, most drugs used to treat illnesses in children have never been formally tested or approved for pediatric use and lack even basic dosage recommendations for children in their labeling. To encourage the research-based pharmaceutical industry to develop specific information about uses and doses of prescription medicines for children, the pediatric exclusivity provision provides an incentive of six months marketing exclusivity which attaches to any existing patent protection.

The results of this provision have been extremely positive. And don't just take my word for it. According to the Clinton FDA "the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date." Between 1991 and 1996, only 11 pediatric studies were completed by the pharmaceutical industry at the request of FDA. After passage of the pediatric exclusivity provision, in three short years the pharmaceutical industry has agreed to conduct 411 pediatric studies in the hope of obtaining the additional six months of exclusivity. Already, there have been 18 label changes for the benefit of children, all at the cost of only one-half of one percent to the nation's pharmaceutical bill.

But we can do better. Because the exclusivity only attaches to drugs with remaining patent protection or exclusivity, many drugs used in children will not be tested because there's no economic incentive to do so. We must ensure that when this provision is reauthorized, we include language which results in these drugs being studied for pediatric uses.

PDUFA represents another success for the American consumer. PDUFA authorized the FDA to collect fees from companies that produce drugs and biologics to hire more reviewers and support staff and upgrade information technology. In 1992, there were 1,277 drug reviewers within FDA, and today that figure has nearly dou-

bled. And the result? Approval times have been cut in half, and the percentage of new drugs introduced in the United States before being introduced in other countries has nearly doubled.

But FDAMA is more than pediatric exclusivity and PDUFA. It represents an effort to have industry and government work more collaboratively in order to speed the decision-making process, and it represents an effort to get better information in the hands of patients, doctors and consumers. I look forward to hearing from the various stakeholders who will testify today to determine whether these reforms are working, and I yield back the balance of my time.

PREPARED STATEMENT OF ANNA ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Thank you, Mr. Chairman, for holding this hearing today. It's hard to believe FDAMA is up for reauthorization already.

I feel like it was just yesterday that we tackled this issue, working night and day to write legislation that would streamline the agency and speed live-saving products to our constituents without sacrificing safety or effectiveness.

As one of the leaders of that effort, I'm proud to see the successes that have resulted.

Medical device and pharmaceutical companies throughout my congressional district consistently applaud the dramatic improvements FDAMA made to the approval process.

Product approval times have been cut in half, bringing cutting-edge, life-saving therapies to patients sooner than ever.

However, I'm concerned that there still may be a few snags.We'll hear from industry representatives today that pre-market approval times are still twice the statutory mandate at 360 days instead of 180.

Agency interpretation of "least burdensome" means to proving safety and effectiveness has been too broadly interpreted and is delaying approval of important patient products.

The Agency has dragged its feet in implementing third party reviews and dispute resolutions—two key provisions of FDAMA.

I look forward to hearing from Ms. Suydam on these issues. However, I must also say that I'm disappointed that President Bush has not yet appointed a FDA Commissioner.

I find it quite disconcerting that the agency entrusted to protect the public health from unsafe food, drugs and devices is still functioning without leadership.

But there's another issue that I'm interested in and look forward to hearing from the witnesses on—reuse of single-use medical devices.

In 1999, after reading several media reports of delicate single-use devices, such as balloon catheters and biopsy forceps, being reused on patients and causing infection and injuries, I contacted the FDA to ask why they weren't regulating this potentially dangerous practice.

The response was less than satisfactory. I was told that the FDA just simply didn't have the resources to regulate this practice and, therefore, was nowhere near developing a policy on reuse.

Faced with an Agency that was failing to act, I introduced legislation to require reprocessed devices to undergo approval for safety and effectiveness. Within a week, FDA issued a proposed regulation, which was finalized last year.

I'm pleased that the Agency finally took action on this important public health issue. Profits should not be put ahead of patients.

I'll be interested to hear from the witnesses how implementation of the regulation is progressing.

Thank you, Mr. Chairman.

PREPARED STATEMENT OF ELIOT L. ENGEL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Mr. Chairman, I want to thank you for calling this hearing today, and I want to thank all of the witnesses for their time and their testimony. We will be discussing one of the most important issues we in Congress face—ensuring the health and welfare of the people of this country as they eat their meals, take their medicine, and use numerous products and devices that they think are safe. But it is not only safety that is at issue today, it is also efficiency and whether or not the Food and Drug Administration (FDA) is reviewing and approving or disapproving submissions in a timely manner, thus ensuring that the best technologies are available to the public.

In 1997 Congress enacted the Food and Drug Administration Modernization Act (FDAMA) to streamline the administrative process in order to get new technologies to the public in a safe and timely fashion. Despite those efforts, we have heard testimony in this committee time and again stressing the need for further reform because there are life-saving medications and devices sitting in storage awaiting FDA action. We are here today to examine the successes and failures in FDAMA to determine what action, if any, is necessary at this time. We will hear testimony praising the success of the Prescription Drug User Fee Act (PDUFA) for cutting review times in half.

We will also hear criticism that PDUFA may compromise safety because of what has been dubbed—a "sweat shop" mentality at FDA to get drugs approved quickly and the possible bias PDUFA has created due to the FDA's reliance on the additional funding it generates. We can also use the knowledge acquired from PDUFA to implement changes in the medical device approval process. That is, would user fees, or some other form of revenue generating provision, enhance the medical device review process. I will inquire about this later when I have the opportunity to question members of our panel.

Pediatric exclusivity is also at issue. There is strong criticism by some suggesting that 6 months of exclusivity is too big a trade-off for testing drugs and dosing them for children. However, we will also hear praise by some for the enormous benefits it has created in pediatric medicine. In fact, we will hear from Dr. Richard Gorman in his testimony about the tremendous gains in pediatric medicine in only 3 years since the exclusivity provision was enacted. Congress must examine these issues closely as certain provisions are set to expire in the coming years. While there may be some fine-tuning needed to some of the FDAMA provisions, we must not undue the gains we have made.

Mr. Chairman, new and innovative technologies are emerging everyday that have the potential to save lives or greatly enhance the quality of life for so many. We in Congress must work with industry and the FDA to enhance current practices to bring products to the public in a safe and efficient manner. While safety must not be compromised, if there are ways to speed-up the administrative process we must consider doing so. We must not let bureaucracy stifle innovation. I look forward to the hearing the testimony from our witnesses and hope to work with you Mr. Chairman and Ranking Member Brown, and the rest of the Members on the Committee to bolster FDA's efforts to safely and effectively carry out its mission.

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

Thank you Mr. Chairman, and thank for holding a hearing today on the effectiveness of the Food and Drug Administration Modernization Act (FDAMA).

Over the past few years, we've heard a lot about the cost of prescription drugs, but very little about the agency that ensures their safety and quality.

But just as important to seniors as a Medicare prescription drug benefit, is ensuring that important, life-saving drugs can are available when seniors need them.

I supported this legislation when it was first introduced in the 105th Congress because I believed it was necessary to improve the process by which the FDA approved pharmaceuticals and biologics.

And by many standards, the legislation has been successful.

But as we begin consideration for reauthorization of FDAMA, I think it is important that we hear from the different parties about what they perceive are the successes and failures of this bill.

There are a number of concerns about the implementation of FDAMA, including the impact of the Prescription Drug User Fee Act (PDUFA).

By many standards, PDUFA has been successful in ensuring that life-saving medications make it to the marketplace as quickly as possible.

The user fees collected through PDUFA have enabled the FDA to speed up the application review process for pharmaceutical and biological products.

In the three years since we last authorized PDUFA, the agency has met almost all of its performance goals. The average approval time for FY 00 was only 11.9 months, down from almost 21 months just five years ago.

But there are some concerns about the effect of PDUFA on product safety

Ensuring that the integrity of FDA's approval process is not compromised is of paramount importance to all Americans, and I am very interested to hear from the FDA regarding measures they have in place to ensure that quality is not compromised in the name of expedience.

I also have some concerns regarding the impact of the performance goals in PDUFA on the culture at the FDA.

A common complaint from both consumer groups and FDA alike, is that "sweat shop" conditions have impacted employees at FDA, prohibiting them from attending continuing education classes, raising their stress levels, and resulting in high turnover.

This environment is not only bad for employees, but it's bad for the process.

Training scientists takes a tremendous amount of time and resources.

The loss of those human resources impacts the ability of the FDA to do its job.

There is also a real shortage of financial resources at FDA.

In a recent Congressional briefing on PDUFA, FDA has expressed concern that PDUFA is crowding out other non-PDUFA programs, such as post market surveillance, approval for generic pharmaceuticals, and oversight of direct-to-consumer marketing.

It is important that the activities at FDA be balanced and that adequate resources are provided to ensure that FDA can meet its mission.

In addition to PDUFA, I am interested to hear from our witnesses regarding other elements of FDAMA, such as the issues surrounding pediatric exclusivity, and the effects it has on the ability of generics to compete.

Studies by HHS have revealed that, while providing exclusivity has improved labeling for children in some areas, it has not gone far enough.

According to HHS, the incentive is not adequate for drugs with low sales volume, off patent products, and the entirety of biologic products.

The incentive has also not been effective for neonatal populations.

Now is a good time to exchange ideas on ways to improve this situation to ensure that all important drugs and biologics are available to children.

Mr. Chairman, thank you again for holding this hearing.

I look forward to hearing the testimony of our witnesses today, and yield back the balance of my time.

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

Mr. Chairman, thank you for scheduling this hearing to evaluate the effectiveness of the Food and Drug Modernization Act (FDAMA). As you know, this law was the bipartisan product of a lot of hard work by our colleagues, our staff, the Senate, the Food and Drug Administration (FDA), and stakeholders.

I agree with those who generally consider FDAMA to be a success. That said, experience shows that every law and program needs periodic review and revision. Though this is our first hearing to review FDAMA, I hope it will not be the last. There are many issues under the auspices of FDA that I would like for us to examine, whether formally styled as oversight of FDAMA, or not. Let me list a few.

For a number of years I have introduced legislation, and soon I will again, to enhance the safety of the nation's imported food supply. We face ever more important challenges in the form of microbial and other food-borne contaminants that strike hardest at the most vulnerable among us. FDA estimates that fully one fourth of America's population is considered to be especially vulnerable to food pathogens due to age (children and the elderly) or health status (weakened immune systems from cancer, organ transplant, HIV infection, and the like). I happen to believe that FDA needs enhanced authority and resources to deal with these challenges.

Then there is tobacco. The Supreme Court threw out FDA's regulation aimed at teen smoking. It is our job to provide FDA with the authority it needs to do its job in this area. Secretary Thompson and even the largest tobacco company, Philip Morris, agree that FDA should have jurisdiction to regulate this product. The issue deserves our time and attention.

Dietary supplements are virtually unregulated, notwithstanding the fact that many of them contain pharmacologically powerful active ingredients. This industry has no good manufacturing practices (GMPs), no mandatory adverse event reporting system, and FDA lacks adequate authority and resources to protect the public from hazardous, even lethal, supplements.

Imported drugs are an increasingly important source of concern. The so-called personal use policy is a sham and millions of Americans are subjecting themselves to great risk in the form of drugs from unknown foreign sources. Congress passed a law last year that could have made things worse. This committee did not report that legislation, nor has it held a hearing on the subject. I think we could perform a valuable service for our colleagues holding hearings about the perils of which I speak.

Also, over the past several years, we have seen several new drugs withdrawn from the market because of the harm they caused. Was it the company's fault? Was FDA lax or overburdened? Are these problems the result of too-quick approval? The Congress would benefit from reviewing these problem drugs more closely.

I look forward to hearing about how the specific provisions of FDAMA are working. Because the pediatric exclusivity provision of section 111 expires at the end of this year, I will be particularly interested in the testimony regarding that aspect of FDAMA. There is apparent consensus that testing and labeling of drugs that are used on children is an important objective. My questions concern the means of achieving that objective.

In examining the six month period of exclusivity provided by current law, or any alternatives to it, I have three questions. First, is the provision effective? Second, is the provision efficient? Third, is the provision equitable? I have concerns with the six month exclusivity incentive on all three counts. So did the Secretary of Health and Human Services in her January 2001 report to Congress, "The Pediatric Exclusivity Provision."

It is clear that exclusivity is not an effective incentive to promote pediatric testing in important pharmaceutical areas. It is not effective for off patent products, it is not effective for small market products, and biologics are not even eligible for the incentive.

The incentive is not efficient in so far as its "one size fits all" aspect conveys a windfall on blockbusters like Claratin that get the same six months as products with vastly smaller sales volume.

Finally, the incentive is inequitable because it is paid for by consumers who use the drug being studied by delaying generic competition for six months. The benefits of pediatric testing are societal, and society, not a relative handful of consumers, should pay its costs.

Given these facts, we should be open to discussing and developing alternatives that meet the agreed upon objective in a better way. I look forward to working with my colleagues and interested parties on this matter.

Finally, I want to say just a general word about the FDA. FDA cannot simply "do the best it can with what it has" in the form of authority and resources. The magnitude and nature of the challenges facing FDA are different today than they were at any time in our history. Resistant microbes, undetectable pathogens, and genetic modifications are but a few of the new challenges to old problems. As one of today's witnesses aptly put it, FDA modernization is a continuous process. We need to be sure we provide the oversight and, where needed, the resources and authority for FDA to be responsive and responsible to the consuming public now and in the future. So again, I express my hope that this will be the first of many hearings that focus on FDA's programs and responsibilities.

Mr. BILIRAKIS. All right. We'll move onto the first panel now. We have Linda Suydam, Dr. Suydam, who is a Senior Associate Commissioner of the Food and Drug Administration. Mr. Steve Northrup, Executive Director of the Medical Device Manufacturers Association, and Dr. Rhona Applebaum, Executive Vice President of Scientific and Regulatory Affairs for the National Food Processors Association.

Ms. Suydam, since you are the Administration witness, we will set the clock to 10 minutes. By all means, please proceed. You all know that your written statement is already a part of the record. We would hope that you would complement it. You are recognized.

STATEMENTS OF LINDA A. SUYDAM, SENIOR ASSOCIATE COMMISSIONER, FOOD AND DRUG ADMINISTRATION; STEPHEN J. NORTHRUP, EXECUTIVE DIRECTOR, MEDICAL DEVICE MANUFACTURERS ASSOCIATION; AND RHONA S. APPLEBAUM, EXECUTIVE VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, NATIONAL FOOD PROCESSORS ASSOCIATION

Ms. SUYDAM. Thank you. Good morning, Mr. Chairman and members of the committee. I am Linda Suydam, Senior Associate Commissioner of the Food and Drug Administration. I am pleased

to be here today to discuss the agency's progress and success in implementing the Food and Drug Administration Modernization Act of 1997.

FDA has made a strong commitment and given high priority to implementing the Modernization Act in a manner that is consistent with both the letter and the spirit of the law. We are well aware that FDAMA, as we call it, is landmark legislation of exceptional significance for the future of the FDA and for the future of the public health in our country. We wish to thank the committee for their thorough, comprehensive work performed in drafting FDAMA. We are particularly appreciative that you based this historic act on the principle that underscores its benefits, that FDAMA made improvements without changing the high public health standards FDA is charged with upholding.

Over the past 3½ years, FDA has worked hard to implement this new law. We have met nearly every statutory deadline. We have issued dozens of regulations, guidance documents, Federal Register notices, and reports to carry out the goal of this wide-reaching law. I ask that my written testimony and supplementary material that expand on the agency's activities to implement the act be included in the record.

Mr. BILIRAKIS. Without objection.

Ms. SUYDAM. Overall, FDAMA has been a success. While the broad statute covers many issues, I would like to focus the committee's attention on two key provisions of FDAMA that will sunset next year and require Congressional action: the reauthorization of the Prescription Drug User Fee Act, PDUFA, and the pediatric exclusivity provision. The pediatric exclusivity provision expires on January 1, 2002, and PDUFA on September 30, 2002.

During the 8½ years of PDUFA, the Agency's performance has met the highest expectations. While adhering to rigorous standards for safety and effectiveness, FDA has met virtually all of the program's review goals. PDUFA I was directed at reducing drug review times. During PDUFA I, FDA exceeded all of its performance goals, and significantly reduced those review times.

PDUFA II included some performance goals to further reduce review times, but many of the performance goals were also directed toward reducing clinical drug development time. These goals included accelerated consultations on critical drug development issues, timely resolution of major disputes, and rapid handling of other clinical drug development issues such as clinical holds.

PDUFA has created significant benefits for the public, industry, and for FDA. Not only has FDA significantly reduced review times and clinical drug development times as a result of the PDUFA programs, but we have also significantly reduced approval times, and therefore, the overall time it takes to get new drugs to the market.

For industry, one measure of PDUFA's advantage is that now nearly 80 percent of new drugs worldwide are first launched in the United States due to the favorable regulatory climate that exists here as opposed to 40 percent prior to the enactment of PDUFA.

FDAMA's pediatric exclusivity provision is also helping to ensure access to and safe use of therapies for children whose treatment has historically been hampered by inadequate information about the safe and effective use of drugs in the pediatric population. Pro-

viding adequate pediatric use information for drugs and biologics has long been a high priority for the Agency. We are pleased to report that the industry's response to the incentives offered by this provision have been enthusiastic.

As you know, in June 1998, we issued written guidance to communicate to the industry our plans for implementation of the pediatric program, and updated this document in October 1999, to provide additional information. The results speak for themselves. Between June 1998, when the guidance document was published, and April of this year, FDA has received over 218 proposed pediatric study requests. Through our ongoing work using mechanisms such as our Pediatric Advisory Subcommittee, we continued to move toward our goal of having adequate pediatric use labeling information for all drugs used in all children. Experience with this provision has also revealed several categories of products and age groups for which this approach has not worked particularly well.

FDA looks forward to working with the committee to reauthorize PDUFA and the pediatric exclusivity provision. We believe that in drafting new authorizing language the following principles should be taken into account. First, FDA's high public health standards must be maintained and enhanced. Second, the integrity of FDA's decisionmaking must be preserved. Finally, FDA must possess an adequate science base for the programs it implements.

I am pleased to report that President Bush's fiscal year 2002 budget for FDA provides for the first time in 7 years, full cost of living increases for FDA employees, and an overall increase of almost 10 percent for the FDA budget. This will enable us to continue to positively meet the challenges of PDUFA.

Thank you for FDAMA. Thank you for the opportunity to be here today. I will be happy to answer any questions you may have. I look forward to working with the committee in the future.

[The prepared statement of Linda A. Suydam follows:]

PREPARED STATEMENT OF LINDA A. SUYDAM, SENIOR ASSOCIATE COMMISSIONER, FOOD AND DRUG ADMINISTRATION

INTRODUCTION

Mr. Chairman, Members of the Committee, I am Linda Suydam, Senior Associate Commissioner at the Food and Drug Administration (FDA or the Agency). I am very pleased to be here today to discuss the Agency's progress and success in implementing the Food and Drug Administration Modernization Act of 1997 (FDAMA or Modernization Act). FDA has made a strong commitment and given high priority to implementing the Modernization Act in a manner consistent with the letter and spirit of the law.

FDAMA is an important addition to FDA's legislative framework. As you know, it was passed after a thorough congressional examination of the Agency's policies and programs; it addressed virtually all of them comprehensively; and it settled a debate about FDA's role by reaffirming the Agency's vital importance for public health protection. This is a law we can all be proud of.

FDA thanks the Committee for the diligent, comprehensive work it performed in drafting FDAMA, and, in particular, for adhering to the principle that underscores the benefits of this legislation; that FDAMA made improvements without changing the high public health standards FDA is charged with upholding. Only by maintaining these high standards and ensuring regulatory decision-making based on sound science can future legislation, such as the reauthorization of the Prescription Drug User Fee Act and the pediatric exclusivity provision, serve to effectively promote and protect the public health consistent with FDA's historic mission.

FDAMA added new mission objectives that call on the Agency to carry out all of its operations—domestic and foreign—in cooperation with its stakeholders. This em-

phasis on FDA's need to extend its regulatory cooperation is so essential for our operations that these objectives are included among the five fundamental principles that offer the best strategy for meeting FDA's formidable challenges in the future. These principles are:

- Base all FDA operations and programs on strong science, as the principal guarantee of the high quality of FDA's public health protection.
- Make regulatory decisions in the context of each product's total life cycle, to ensure its safety and effectiveness when it is in wide use.
- Consider our decisions also from a global perspective, to take into account the numerous international developments and factors that affect public health in the United States (U.S.).
- Use leveraging as the primary means for maximizing the effects of FDA's actions.
- Maintain FDA's traditionally high public health standards, because they always will be critical for ensuring effective health care delivery, consumer confidence, and a level playing field for the competitiveness of U.S. industry.

Over the past three and one-half years, FDA has worked diligently to implement this new law, which, as we stated, touches nearly every aspect of the Agency's mission.

We have met nearly every statutory deadline, issued dozens of regulations, guidance documents, Federal Register notices, and reports to carry out the goals of this wide-reaching law (see Attachment).

I would like to begin with two key provisions of FDAMA—reauthorization of the Prescription Drug User Fee Act and the pediatric exclusivity provision. The pediatric exclusivity provision will expire on January 1, 2002, and the fee authority of the Prescription Drug User Fee Act will expire on September 30, 2002. Maintaining these authorities is important to the Agency, and we look forward to working with the Committee during the reauthorization process.

PRESCRIPTION DRUG USER FEE ACT

The most concrete expression of the leveraging principle in FDAMA was the reauthorization for five more years of the Prescription Drug User Fee Act of 1992 (PDUFA). As you know, PDUFA authorizes FDA to receive manufacturers' user fees in return for achieving performance goals agreed to by Congress, the pharmaceutical industry and our Agency. The result is expedited access to a greater number of important new therapies. PDUFA is nearing the end of its second five-year term and, therefore, I will examine in greater depth our experience with PDUFA I and II.

During the eight-and-a-half years of PDUFA, the Agency's performance has met the highest expectations. While adhering to rigorous standards for safety and effectiveness, FDA has met virtually all of the program's review goals. PDUFA I was directed at reducing drug review times. During PDUFA I, FDA exceeded all of its performance goals and significantly reduced review times. PDUFA II included some performance goals to further reduce review times, but most of the performance goals were directed towards reducing clinical drug development time. These goals included accelerated consultations on critical drug development issues, timely resolution of major disputes, and rapid handling of other clinical drug development issues such as clinical holds.

Under PDUFA II, FDA has exceeded almost all of its performance goals resulting in a continued reduction in review times. In addition, drug development times also have decreased significantly. According to the Tufts Center for the Study of Drug Development, the clinical development time for new molecular entities declined by 22 percent from the early to the late 1990s.

Not only has FDA significantly reduced review times as a result of the PDUFA programs, but it has also significantly reduced approval times, and, therefore, the time it takes to get new drugs to market. Total approval time is the time from the initial submission of a marketing application to the issuance of an approval letter for that application. It includes both FDA's review time and the time the sponsor spends answering deficiencies noted by FDA and can encompass several review "cycles."

The median total approval time for new drug and biologic applications submitted in Fiscal Year (FY) 1999 dropped to 11.6 months from 20.1 months in FY 1994. Given the progression of PDUFA II review goals, median total approval times could drop to 10 months in FY 2001 or FY 2002 if the current rate of first review cycle approvals is sustained.

Median total approval time for priority applications submitted in FY 1999 was six months, less than half the median total approval time for priority applications submitted in the early PDUFA years. Priority applications, a subset of all applications, have a PDUFA review performance goal of six months.

Drugs are now reviewed in the U.S. as fast or faster than anywhere in the world, without compromising the very stringent standards that Americans have come to expect. This is remarkable, particularly in light of the fact that over the past seven years, pharmaceutical firms have introduced 234 new molecular entities into the market—a sizable increase over prior decades. Although European pharmaceutical companies dominated the industry ten years ago, U.S. companies now have an overwhelming lead in world markets.

Let me take a moment to mention the products themselves. Drug and biologic approvals in 2000 included a large number of products that represent significant advances over the products that were previously available. Important new therapies brought to market in the past year include: three new drugs to treat cancer; the first protease inhibitor approved to treat HIV infection in children as young as six months; four drugs to treat heart disease and circulatory disorders of the nervous system; a malaria treatment effective in areas where the disease is resistant to other anti-malarial drugs; the first anti-inflammatory corticosteroid that can be used in a nebulizer by very young children; the first in a new class of antibiotics; a treatment of cancer-in-situ in the absence of associated invasive cancer of the bladder; the first multivalent conjugate pneumococcal vaccine for infants and toddlers under the age of two; the first drug to reduce the severity of neck and shoulder muscle contractions and the resulting abnormal head position and neck pain associated with cervical dystonia; the first thyroid replacement drug to undergo a stringent FDA review; three new drugs and five new uses of existing drugs for "orphan" patient populations of 200,000 or fewer; and 13 new pediatric uses for already approved adult drugs.

In the biotech area, 2000 saw the approval of products that delay the time to disease progression in malignant osteopetrosis; reduce the signs and symptoms of rheumatoid arthritis in patients with inadequate response to methotrexate; and delay structural damage in patients with moderately to severely active rheumatoid arthritis. These are only a few exciting examples of products that are being made available to the patients who need them.

For the industry, PDUFA provides huge benefits:

- Drug companies' products are able to take fuller advantage of granted patent terms, which yields additional revenues, because they come on the market more quickly due to shorter development and review times.
- The development of guidance documents, earlier meetings and increased FDA reviewing staff have made the processing of submissions more understandable and predictable, and therefore provide a more consistent and dependable basis for companies to develop plans for production and other activities.
- In addition, FDA's guidance and consultation received by drug sponsors under PDUFA help them improve the quality of their product applications, which reduces the cost of drug development.

One measure of these advantages to the industry is that between 1996 and 1998, nearly 80 percent of new drugs world-wide were first launched in the U.S. due to the favorable regulatory climate.

For FDA, PDUFA has also brought significant benefits:

- The performance goals have helped streamline the management of drug and biological product reviews.
- The program's requirement for comprehensive product reviews and responses has resulted in improved quality of the application process.
- Most important of all, the fees have enabled the Agency to hire additional medical and other specialists, and to upgrade the technology that is essential for the success of the program.

PDUFA has provided the Agency with some challenges. Between 1994 and last year, the number of review goals to be met by FDA has tripled. The number of PDUFA submissions has grown by 64 percent, from not quite 1,500 in FY 1993 to almost 2,500 in FY 2000. In addition, there are other industry meeting and procedure goals in PDUFA that add up to more than 3,500 FDA actions a year, most of which occur before an application submission (and fee collection). These actions are connected with the preparation, scheduling, conduct, follow-up and tracking of formal meetings requested by industry that may involve as many as 10-20 FDA staff and 15-30 industry representatives. Another notable trend has been the upsurge in drug advertising directed to consumers (DTC) and physicians.

PEDIATRIC EXCLUSIVITY

FDAMA's pediatric exclusivity provision in section 111 (section 505A of the Federal Food, Drug, and Cosmetic Act), like PDUFA, is also scheduled to sunset in 2002. FDAMA's pediatric exclusivity provision is helping to ensure access to, and

safe use of therapies for children whose treatment has historically been hampered by inadequate information about the safe and effective use of drugs in the pediatric population. Providing adequate pediatric use information for drugs and biologics has long been a high priority for the Agency. We are pleased to report that the industry's response to the incentives offered by this provision has been enthusiastic. As you know, in June 1998, we issued written guidance to communicate to industry our plans for implementation of the pediatric program, and updated this document in October 1999, to provide additional information to industry.

The results speak for themselves. Between June 1998, when the guidance document was published, and April 1, 2001, FDA has received over 218 proposed pediatric study requests. Through our ongoing work using mechanisms such as our Pediatric Advisory Subcommittee, we will continue to move toward our goal of having adequate pediatric use labeling information for all drugs used in children.

The purpose of encouraging pediatric studies is to provide needed pediatric efficacy, safety and dosing information to physicians in product labeling. Of the 28 drugs granted pediatric exclusivity, 18 drugs have newly approved labeling for pediatric use. Labeling changes are expected approximately 6-12 months after the studies have been submitted. Of the 18 drugs whose labels have already been changed, four were new molecular entities for which pediatric labeling was available at the time of initial approval. The 14 remaining marketed products now have complete labeling in the relevant pediatric population.

Studies of six of these products resulted in identification of significant changes in dosing or adverse events either specific to or newly defined in the pediatric population.

Two examples of these clinical findings are:

- Midazolam (Versed)—higher risk of serious life threatening situations in children with congenital heart disease and pulmonary hypertension who need lower doses than predicted to prevent respiratory compromise;
- Gabapentin (Neurontin)—need to use higher doses in children less than five years of age in order to control seizures and new adverse events such as hostility and aggression identified in children less than 12 years old.

As required by the pediatric exclusivity provision, the Department issued a report to Congress in January 2001, on the experiences under the new law. The Report stated that the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date. Experience with the provision has also revealed several categories of products and age groups for which this approach has not worked. For example, the exclusivity provision does not address the drugs that have no patent protection and sponsors have no economic incentive to study these products.

FDA looks forward to working with the Committee to reauthorize PDUFA and the pediatric exclusivity provision. FDA believes that when drafting new authorizing language, the following principles should be taken into account:

- FDA's high public health standards must be maintained and enhanced.
- The integrity of FDA's decision-making must be preserved.
- FDA must possess an adequate science base for the programs it implements.

IMPLEMENTATION OF OTHER FDAMA PROVISIONS

With the tools provided by FDAMA, FDA is becoming a stronger, better Agency, one whose actions remain firmly based in science to promote and protect the public health.

The value of a strong, science-based FDA cannot be overstated—it reaps public health benefits for both individual citizens and the nation as a whole. An FDA that sets and meets high scientific standards provides a high level of assurance to our citizens; (1) assurance that product risks are minimized; (2) assurance that consumers receive reliable information to assess and manage the remaining risks in concert with a health professional, or on their own; and (3) assurance that reviews for new products are conducted in a predictable and timely manner, giving patients early access to new safe and effective products.

FDA's procedures should provide consumers with confidence in the decisions it makes about the products that they take and give to their families, and provide industry with the confidence that the Agency's decisions are fair and based in science.

From an economic standpoint, a strong, high-performance FDA stimulates innovation, enhances U.S. competitiveness in global markets, provides a level playing field for industry, and strengthens the domestic economy as a whole by inviting increased foreign investment and contributing to reduced health care costs.

I would like to focus today on how FDA's implementation of the Modernization Act is helping to enhance the public health by producing the following outcomes: (1)increase access to new medical products; (2) provide more effective management of FDA's limited resources; (3) make our regulatory processes more effective and efficient; and (4) increase consumer and industry confidence through collaboration.

ACCESS TO MEDICAL PRODUCTS

There are a number of FDAMA provisions, in addition to PDUFA and pediatric exclusivity, that help ensure greater patient access to medical products.

Fast Track

The first of these is the fast track provision in section 112. In the fast track provision, Congress codified FDA's accelerated approval regulations and thus codified our approach to expedited drug development. Fast track is meant to facilitate the development, and expedite the review, of drugs that are intended to treat a serious or life-threatening condition and that demonstrate the potential to address a serious unmet medical need.

Since the passage of the Modernization Act, we have granted fast track designation to a wide range of therapies—not just for AIDS and cancer drugs, as some believe, but for drugs to treat atherosclerotic vascular disease, acute stroke, diabetes, adult respiratory distress syndrome and pancreatitis, and genetic abnormalities of infants. As of March 2001, FDA's Center for Drug Evaluation and Research (CDER) had received 108 requests for fast track designation—69 were granted, 25 denied, and 14 are still pending. As of March 31, 2001, FDA's Center for Biologics Evaluation and Research (CBER) had received 62 requests for fast track designation—38 were granted, 23 denied, and one is still pending.

Since we began implementing this provision, CDER and CBER have approved nine novel products, including Herceptin, a monoclonal antibody for metastatic breast cancer (in 4.7 months), Enbrel for rheumatoid arthritis (in 5.8 months), Ziagen for HIV (in 5 months), and Pneumococcal Conjugate Vaccine for the prevention of streptococcus pneumoniae in infants and children (in 7.5 months). In addition, three marketed products were approved for new indications under the fast track program: Remicade for rheumatoid arthritis, Gamma interferon for osteopetrosis, and Taxotere for non-small cell lung cancer. As implemented by FDA, this program is plainly helping to ensure that important therapies for serious and life-threatening illnesses are being brought as quickly as possible to the patients who need them.

To provide clear information to industry regarding participation in the fast track process, last fall we issued a guidance document that defines the criteria for qualification for the fast track drug product development program, sets out the process for designation as a fast track drug product, and describes programs for expediting development and review of fast track products. The Agency has received feedback that commends this document as an excellent resource for sponsors who are interested in receiving fast track designation for their products.

Supplemental Applications

Just as it is important to get the most complete information about all patient populations on a drug's label, it is also important to get all of the information about a drug's uses on the label. This is why Congress directed FDA to take steps to encourage the submission of supplemental applications for new uses for approved medical products, and steps to ensure that such applications are acted upon expeditiously. Since enactment, the Agency has made programmatic changes in CDER, CBER, the Center for Devices and Radiological Health (CDRH), and the Center for Veterinary Medicine (CVM) to encourage supplemental applications for new uses, and ensure that the Agency acts on the applications that it receives in a timely manner. The Agency has also issued guidance that clarifies what is needed to demonstrate effectiveness for a new use.

Expanded Access to Investigational Therapies

Congress and FDA realized that there are times when a patient's interest is best served by getting an investigational medical product as quickly as feasible, sometimes before a complete evaluation and review can be finished. The expanded access provision (section 402) of the Modernization Act was included in the legislation to facilitate access by patients with serious or life-threatening illnesses to promising, yet unapproved new products. By codifying and expanding this program, the statute ensures that this program will continue to provide expanded access to patients in the future.

Humanitarian Use

Congress also recognized that there are limited circumstances when there are too few subjects to justify a full-scale evaluation of a medical device. The humanitarian use device provision (section 203) provides an easier path to market for devices used to treat rare conditions or diseases. Under this provision, a manufacturer is not required to meet the effectiveness requirements in the statute, but rather must show that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk from its use. Since implementation of the Modernization Act, CDRH has approved 21 humanitarian use devices, including: a fetal bladder stent, to treat urinary tract obstruction in unborn babies; an electrical bladder stimulator for urinary incontinence for use in children for the treatment of neurogenic bladder disease secondary to spina bifida; a pulmonary valve for children under age four with absent or diseased valves; and an extracorporeal immunoabsorption system for treatment of patients with hemophilia A and B who have inhibitors to Factor VIII and IX coagulation factors.

Postmarketing Studies

On April 30, 2001, FDA's regulations implementing section 130 of FDAMA which requires sponsors of approved drugs and biologics to report annually on the status of postmarketing commitments became effective. These regulations modified existing reporting requirements for new drug application (NDA) drug studies and created a new reporting requirement for biologic products.

FDA may request postmarketing studies to provide additional important information on how a drug works in expanded patient populations or to identify safety issues that occur at very low frequency or in special patient populations. In the case of drugs and biologics approved under accelerated approval regulations, postmarketing studies are performed to confirm a drug or biologic's long-term clinical benefit when approval was granted based on studies using surrogate endpoints.

These new regulations were of special interest to patient and consumer advocates who were concerned about timeliness of applicants in completing postmarketing commitments and of FDA in reviewing study results and modifying drug labeling. The regulations will provide FDA with a mechanism to monitor study progress through the annual submission of study status reports. FDA will post the status of postmarketing studies on its public website and publish in the Federal Register an annual summary of industry progress in fulfilling postmarketing commitments. FDA has committed to timely review and evaluation of completed studies and to requiring timely modification of drug and biologic labeling where appropriate.

EFFECTIVE MANAGEMENT OF FDA RESOURCES

Part of meeting the Agency's mission to protect and promote the public health involves effective management of FDA's resources. There are several FDAMA provisions that reduce the Agency's workload in some areas so that those resources can be provided to areas with the greatest public health risk.

Third Party Review

One such provision is the device third party review program (section 210), which provides an alternative review mechanism for low-to-moderate risk devices, thereby allowing FDA to target its scientific review resources on higher-risk devices. There are currently more than 670 types of devices eligible for review by third parties, and 12 accredited third party organizations. CDRH recently expanded the program to include all devices eligible for review by third parties under the statute and has been working with industry representatives to encourage greater use of this new approach.

User Reporting

Another provision that allows the Agency to focus its resources is section 213, device user reporting. Prior to passage of FDAMA, all device user facilities were required to report serious adverse events to FDA. Under FDAMA, FDA now has authority to establish a sentinel system for user reporting, which would have a representative sample of hospitals and other user facilities reporting serious adverse events to FDA. The Agency has already conducted a pilot sentinel system, which was very successful. FDA is working to put an expanded sentinel system in place. This initiative could ultimately ease the reporting requirements for user facilities and enhance the value of reports the Agency receives.

MORE EFFICIENT AND EFFECTIVE REGULATORY PROCESSES

FDAMA includes a number of provisions that streamline and expedite FDA's product review processes by ensuring that sponsors know what is required, and by

eliminating unnecessary requirements. Clearly, PDUFA helps the Agency make decisions in a more timely manner. At the same time, PDUFA and other aspects of the statute ensure that FDA's decisions are consistent and predictable. FDA's regulatory requirements are clarified, providing industry with information on how to most effectively comply with the applicable laws.

Meetings with Sponsors

Both as part of the PDUFA agreement formalized as part of the PDUFA performance goals and as part of a separate FDAMA requirement (section 119), the Agency is committed to meeting with drug sponsors to discuss and reach agreement on the design and size of clinical trials. Any agreements reached can only be changed under limited circumstances. Similarly, the device provisions provide for early meetings with potential sponsors to focus on the type of valid scientific evidence needed for device approval and to reach agreement on a study plan. These provisions are ensuring that industry knows up front what is required and does not waste time conducting unnecessary studies.

In addition, many provisions of the Modernization Act are premised on the principle that regulatory requirements should not exceed what is required to promote and protect the public health.

Premarket Notification

An example of matching regulatory requirements to meet public health risk is the premarket notification provision in section 206. More than 75 Class II types of medical devices have been exempted from premarket notification requirements, enabling manufacturers to get their products to market and the patients who need them more rapidly. The types of devices exempted include: clinical laboratory equipment and test kits, kidney stone dislodgers, clinical thermometers, biofeedback devices and physical rehabilitation devices. In addition, pursuant to this section, all but a limited number of reserved Class I devices are also exempt from 510(k) premarket notification.

Manufacturing Changes

FDAMA also streamlines the process for drug and device sponsors to make changes to certain manufacturing processes. For example, the provision on scope of review in section 205 permits device manufacturers to notify FDA 30 days before instituting certain types of manufacturing changes instead of submitting a premarket approval (PMA) supplement. This means that the device manufacturer can often start marketing a device made under this new process at least five months sooner than usually would have occurred before FDAMA. The device industry has already used this provision 215 times. The drug provision permits drug manufacturers to make minor and moderate manufacturing changes without prior approval of a supplemental application. The biologics industry has submitted 2623 notifications of changes requiring a supplement submission 30 days prior to distribution of the product made using the change. In addition, industry has submitted 482 notifications of changes requiring a submission that may be implemented as soon as the submission is made.

Least Burdensome Means

Section 205 of FDAMA is similarly premised on the principle that regulatory requirements should not exceed what is required to promote and protect the public health. This provision requires FDA, in consultation with the applicant, to consider the "least burdensome" appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval. The requirement to consider the least burdensome means applies to both existing statutory paths to market: premarket notifications (510(k)s) and premarket approval applications (PMAs and Product Development Protocols). While FDAMA does not change the standards for premarket review, it clarifies that the Agency's review is to support the substantial equivalence or safety and effectiveness of medical devices.

To foster a collaborative approach to the implementation of section 205 of FDAMA, CDRH hosted a meeting with stakeholders on January 4, 1999, to solicit comments and suggestions regarding the least burdensome approach to medical device development and evaluation. CDRH heard formal presentations at that meeting and also received written comments. As a result of communication with our stakeholders, FDA determined that the issue of highest concern is when clinical data would be required for devices.

In January of 2000, CDRH formed a Least Burdensome Steering Committee consisting of senior managers within the Center. In addition, representatives of FDA participated in a Least Burdensome Industry Task Force aimed at addressing the least burdensome provisions. The Agency has been reporting the results of this col-

laborative effort on FDA's website so that interested parties can contribute their ideas and track FDA's progress in this area. While the main focus of the group has been in developing and articulating the concept and principles that underlie the least burdensome requirement, several guidances have been developed to help reduce unnecessary burdens in bringing new devices to market. All of these guidances are on our least burdensome website. Most recently, the Center completed a draft guidance entitled, "The Least Burdensome Provisions of FDA Modernization Act of 1997: Concept and Principles." This document, which contains the Agency's interpretation of the least burdensome provisions, will be posted shortly on FDA's website.

While developing the guidance, FDA has been working to implement these provisions. Training sessions for CDRH staff and advisory committee members have been conducted and will be expanded once the new guidance is final. Even without a final guidance, however, FDA has many examples of successful use of the least burdensome approach. For example, FDA reviewers approved a pediatric indication for a marketed cardiac ablation catheter without requiring a prospective clinical study because reviewers determined that existing literature supported the device's safety and effectiveness in children. Patient registries and literature were also used to support the approval of a bone cement for fixation of a hip prosthesis.

Abbreviated Study Reports

Another example of process improvements is the provision on data requirements in section 118, which directs FDA to issue guidance on when abbreviated study reports may be submitted in NDAs and biologics license applications (BLAs), in lieu of full reports. On September 13, 1999, FDA published a final guidance that describes when abbreviated reports and synopses can be used to submit effectiveness data. This guidance not only provides clarity, it should also ensure that industry is not submitting more information than is required by the Agency.

Device Standards

Congress and FDA also recognized that industry's ability to rely on standards will help to streamline the approval or clearance of medical devices. Under the provision on device standards in section 204, CDRH recognized more than 567 consensus standards that manufacturers may use to satisfy portions of device review requirements, thus simplifying and expediting product review. Of these 567 recognized standards, over 100 were proposed by industry for recognition as a result of active solicitation by CDRH. A few examples of consensus standards nominated by industry and recognized by CDRH include: standards that can be used to describe and select the necessary biocompatibility testing; most American Dental Association specifications for dental materials and devices; and certain standards for safety requirements for electromedical equipment, covering over 30 individual standards on mechanical limits electrical safety considerations for electrically powered devices.

At the same time, CDRH is trying to broaden the impact of the standards recognition program mandated by FDAMA. CDRH is enlisting its stakeholders in setting priorities for developing standards that can be recognized in the future and encouraging manufacturers to incorporate recognized standards as part of their product specifications, which allows extremely brief product descriptions, and thus, less lengthy 510(k)s.

Single Biologics License

In addition, FDAMA has helped to streamline the processes for submissions from industry by codifying the modernization of certain biologics regulations. In October 1999, FDA issued a final rule to implement the modernization of regulations provision in section 123, which requires manufacturers to make a single submission for a biologics license, instead of separate applications for the establishment license and the product license. When FDA first proposed to streamline the biologics application process for specified products, industry representatives indicated that the change would result in considerable savings of time and money. Since the implementation of the single application/single license approach, industry representatives have confirmed this to be the case.

Dispute Resolution

While many of the provisions in the Modernization Act are designed to facilitate agreement between FDA and industry on regulatory requirements, inevitably, there will be disputes that remain. Section 404, the provision on dispute resolution, requires the Agency to clarify the processes for resolving scientific disagreements, including requests for advisory panel review. While our existing regulations and procedures have worked well to resolve many disagreements, the Agency is taking steps to enhance its dispute resolution processes.

First, the Agency revised Title 21, Code of Federal Regulations section 10.75 to clarify the availability of review of scientific disputes by an advisory panel. CDRH created a medical devices dispute resolution panel, and issued a draft guidance that describes how that panel will be used to resolve scientific disputes. CDRH also issued a general guidance document that provides an overview of all of the Center's dispute resolution processes and has appointed a CDRH ombudsman. CDER and CBER have developed guidance to explain their processes as well.

CONSULTATION WITH CONSTITUENCIES

We have worked to ensure that everyone affected by the Agency's actions has a voice, and that each voice is heard. While all of these voices may not share the same viewpoint, we have found that this open discourse can engender confidence.

FDAMA has contributed significantly to the Agency's effort to collaborate in a credible and reliable way with our constituencies. For example, section 406(b) of the Modernization Act directs the Agency to consult with our constituencies to ensure that we fulfill our statutory mandates and that we communicate clearly with our stakeholders. We have held a series of meetings, during which we have listened to those outside the Agency. We hosted a national interactive videoconference that was simulcast to interested parties in eight different cities. During our national broadcast, we had senior staff at each of the locations to hold a more focused communication with members of consumer groups and the regulated industry in these areas of the country. During these meetings, we received useful feedback on the Agency's performance, as well as constructive suggestions as to how the Agency can continue to improve.

Public Meetings

Finally, FDA has held many public meetings to discuss implementation of specific provisions. For example, CDER and CBER have held several public meetings on implementation of certain provisions. These include four public meetings on the implementation of the positron emission tomography (PET) provisions, three public meetings on the radiopharmaceuticals provisions, and advisory committee meetings on pharmacy compounding.

CONCLUSION

FDA has been fully committed to implementation of FDAMA. However, while devoting time, energy, and resources to this effort, we also have worked to meet our other responsibilities. They include: protecting the safety of the nation's food supply and blood supply, reviewing new food additives to ensure their safety, speeding our reviews of new generic drugs and medical devices and developing a comprehensive regulatory strategy for dietary supplements—which involves the implementation of another complex statute.

I am proud of the work that the Agency has done in fulfilling our FDAMA commitment to Congress and to the American people, and I hope that you share this sentiment. Thank you for the opportunity to be here today.

Mr. BILIRAKIS. Thank you very much, Doctor.

Mr. Northrup?

Mr. NORTHRUP. Thank you.

Mr. BILIRAKIS. Five minutes, sir, or in that category.

STATEMENT OF STEPHEN J. NORTHRUP

Mr. NORTHRUP. Chairman Bilirakis, and members of the subcommittee, I thank you for the opportunity to speak with you today. My name is Steven Northrup. I am the Executive Director of the Medical Device Manufacturers Association based here in Washington, DC.

MDMA is the national voice for the entrepreneurial sector of our industry. The association was founded in 1992 by a group of entrepreneurs who needed a forceful and independent voice in the Nation's capital. Two-thirds of the 6,000 companies in our industry employ fewer than 50 people. But these entrepreneurs are widely acknowledged as the source of most of the breakthroughs in medical technology. Our role in MDMA is to work with the Congress

and with our regulators to ensure that medical device entrepreneurs have a commonsense and equitable regulatory environment in which to innovate.

We are pleased the subcommittee is holding this hearing. I am sure most of you recall the difficulties our industry was experiencing with the FDA in the early 1990's. To your credit, you took decisive action by passing FDAMA, which established or expanded a number of new initiatives designed to improve the regulatory climate for medical products. For your efforts, I extend our members' deepest appreciation.

I am pleased to inform you today that from our perspective, the FDA generally has done a commendable job of implementing FDAMA. Average product review times are down significantly since the mid-1990's, though the FDA still has some work to do to meet its statutory deadlines. The industry's relationship with the FDA also has become less contentious. Most importantly, we have made these improvements without compromising patient safety. Much of this is due to the leadership of people like Dr. Suydam and of Dr. Feigal, who directs the FDA's Device Center.

Despite our general satisfaction, there remain a few areas where continued effort is needed. In our written statement, I have described our concerns about the FDA's implementation of some of these key provisions on third party review of marketing applications, on the resolution of scientific disputes, and on determining the least burdensome pathway to market.

Frankly, the Agency's implementation of these provisions has been slow and remains incomplete. While the specific circumstances of each of these situations are different, the instances collectively call into question the Agency's commitment to implementing all of FDAMA. In our mind, there were no insignificant aspects of that law.

Now to be fair, the FDA has taken positive steps recently on each of the issues I raised in our testimony. As an industry, we are willing to leave the past behind and to move forward with the Agency on these important initiatives. Nevertheless, the problems highlight the need for the subcommittee to continue its careful evaluation of FDAMA, and to hold the FDA accountable for its proper implementation.

Our experience also has taught us that the modernization of the Agency cannot be achieved fully through just one piece of legislation. The modernization of the FDA should be a continuous process directed toward ensuring that the FDA has the tools, the structure, the talent, and the culture to deal with a world in which the pace of innovation is ever increasing.

For example, there are a number of products on the horizon that blur the traditional lines between devices, pharmaceuticals, and biologics. The development of stents coated with drugs that inhibit the tissue growth that causes arteries to re-narrow after angioplasty, a condition called restinosis, suffered recently by Vice President Cheney, is one rather high profile example of a combination product upon which scientists, engineers, and physicians are currently working.

We believe combination products like this don't fit neatly into the FDA's traditional regulatory structure, which reflects the different

laws and standards that govern the review of drugs, of devices, and of biologics. To avoid regulatory delays, we need to prevent jurisdictional disputes or inefficient review processes that result from disagreements on how to regulate these hybrids.

One way that Congress could address this issue is by directing the FDA to establish an Office of Combination Products. Such an office should have the authority to manage the review of a combination product and to coordinate all necessary involvement by the various FDA centers. We believe this would improve the process and reduce the likelihood that clashing regulatory structures within the FDA will delay the review of future combination products.

Drug-coated stents are but one example of the wave of innovation for which the FDA must prepare itself. To help prepare the Agency for the challenges it will face in this new century, MDMA and the other national device industry associations are working together to develop a series of legislative proposals for your consideration. The ideas we are developing, such as the one I have outlined, all are aimed at enabling the FDA to use its resources more efficiently, at augmenting the expertise of the Agency's staff, and at assuring the FDA's accountability for its actions.

We look forward to sharing our ideas with you soon, and to working with you on the continued modernization or more appropriately futurization of the FDA. Thank you for this opportunity to speak with you. I look forward to your questions.

[The prepared statement of Stephen J. Northrup follows:]

PREPARED STATEMENT OF STEPHEN J. NORTHRUP, EXECUTIVE DIRECTOR, MEDICAL DEVICE MANUFACTURERS ASSOCIATION

Chairman Bilirakis and members of the subcommittee, I thank you for the opportunity to speak with you today about the implementation of the Food and Drug Administration Modernization Act of 1997 (FDAMA), as well as some issues the subcommittee should consider as it evaluates the future challenges faced by this agency. My name is Stephen Northrup, and I am the executive director of the Medical Device Manufacturers Association (MDMA), based here in Washington, DC.

MDMA is the national voice for the entrepreneurial sector of the medical device industry. The association was created in 1992 by a group of business executives who believed that the innovative and entrepreneurial sector of the industry—an industry in which most companies employ fewer than 50 people—needed a forceful and independent voice in the nation's capital.

To support these entrepreneurs, our 150 member companies work together with us to ensure that the federal government does not burden innovators with unnecessary or unwise laws or regulations. While we recognize and support the federal government's role in protecting the public health, we also believe government regulation should not prevent or hinder the development of truly beneficial new therapies nor deprive patients of the latest advances in medical care.

As you know, the medical device industry is an integral component of the good health of the American public. The technological innovations and breakthroughs developed by medical device manufacturers have produced the wonders of modern medicine and surgery. Simply put, medical technology enables millions of Americans to live longer, more comfortable, and more productive lives.

Entrepreneurs play an important role in the development of these medical innovations. As I mentioned earlier, two-thirds of the 6,000 companies in our industry employ fewer than 50 people. Nevertheless, these enterpreneurial firms are widely acknowledged as the source of most of the major breakthroughs in medical technology.

The entrepreneurs in our industry have different needs than do the large companies. Fair, predictable, and consistent regulatory actions provide the necessary environment in which entrepreneurs can make best use of the natural advantages they have over their larger competitors—their focus, creativity, and adaptability. The large companies possess two things, however, that these entrepreneurs do not have—time and resources.

Therefore, when the regulatory system is unclear, unpredictable, or unfair, this negates the natural advantages of entrepreneurs. As in most industries, when the regulatory process becomes more of a "game" than a system, the winners will be those companies that have the time and resources to "play the game." MDMA's role in all of this is to work with the Congress and with our regulators to ensure that medical device entrepreneurs have a common-sense and equitable regulatory environment in which to bring their innovations to market.

We are pleased that the subcommittee is holding this hearing to evaluate the effectiveness of FDAMA. The development and passage of FDAMA is largely responsible for stimulating an era of responsiveness and cooperation on the part of our industry's main regulator, the Food and Drug Administration (FDA). For the new members and staff on this subcommittee, I will walk back in time several years to highlight the importance of the legislation we are discussing today.

In the early 1990s, the outlook for medical device innovators and entrepreneurs was grim. New and improved products languished in long review queues and backlogs at the FDA. The relationship between the industry and the agency was adversarial, and communications were poor at every level. Companies were moving their research and development overseas and conducting their clinical studies in countries where regulatory approval was more timely. The FDA simply did not seem to recognize the negative effect that its policies were having on the health of the American public, who watched as patients in Europe and elsewhere reaped the benefits of American ingenuity first, if not exclusively. The hearings this subcommittee held during those dark days are rife with examples of important medical products developed by American companies but unavailable then to American patients.

Fortunately, many members of Congress saw the impact of the FDA's actions (or lack thereof) on the medical technology industry and the patients we aim to serve. In response, Congress passed FDAMA, which established or expanded a number of new initiatives designed to improve the regulatory process for medical products. In addition, Congress recognized that the FDA should be charged not only with protecting the public health, but also with promoting it by facilitating access to new therapies. FDAMA was the vehicle for updating the agency's mission to reflect the new role Congress expected the agency to take. For your efforts, I extend our members' deepest appreciation.

MDMA'S GENERAL PERSPECTIVE ON FDAMA IMPLEMENTATION

I am pleased to inform you that, in general, the FDA's Center for Devices and Radiological Health (CDRH) has done a commendable job of implementing the medical device provisions of FDAMA. From the most critical and bottom-line perspective-how long does it take the FDA to determine a reasonable assurance of the safety and effectiveness of a new product?—the numbers tell a story of great improvement.

According to CDRH's most recent annual report, the center reviewed 4,397 premarket notifications (also known as 510(k) submissions) in fiscal year 2000, slightly less than the 4,593 reviews completed during the previous year. The center's average review time was 77 days, the shortest average time in more than a decade, and well within the statutory 90-day requirement.

Average total elapsed time to premarket approval (PMA), which is required for more complex or higher-risk devices, was 362 days in fiscal year 2000, a 54 percent reduction from the "peak" time of 788 days in fiscal year 1996. While this is an improvement, we are still far from the statutory requirement of 180 days for PMA applications.

The working relationship between the medical device industry and the FDA also has improved since the passage of FDAMA. A survey conducted in 1999 by PricewaterhouseCoopers LLP and CONNECT, the University of California at San Diego's Technology and Enterpreneurship Program, found that communications in general between life sciences companies and the FDA have improved significantly since 1995, when the organizations first began their bi-annual survey. For instance, the 1999 survey found that the percentage of respondents who believed their company's communications with the FDA were "excellent" increased from 34 percent in 1995 to 47 percent in 1999, and the percentage of respondents who indicated that contacts with FDA reviewers were "easy" or "very easy" rose to 64 percent in 1999 from 52 percent in 1995.

At this point, I should note that there is no evidence to suggest that faster reviews of medical devices and a more collaborative relationship between industry and the FDA have come at the expense of patient safety. It's important to remember that increasing regulatory efficiency, not lowering standards, was the goal of FDAMA.

SPECIFIC PROBLEMS WITH FDAMA IMPLEMENTATION

Despite our general satisfaction with the implementation of FDAMA, there are still a few areas where continued effort is needed. These areas include provisions that we consider to be cornerstones of FDAMA, and for which the FDA has not implemented the letter or the spirit of the law as fully as we believe the Congress intended. Three of these are the provisions on third-party review of marketing applications, on dispute resolution, and on arriving at the "least burdensome" pathway to market.

Third-party review (Section 210)

To begin with, the subcommittee should know that the FDA took more than three years to implement fully the third-party review provisions of FDAMA, which directed the FDA to accredit third parties in the private sector to conduct the initial review of 510(k) submissions for low-risk (Class I) and moderate-risk (Class II) devices.

You may have heard that manufacturers have been slow to utilize the third-party review program, and that is true. During the first 17 months of the FDAMA third-party review program, third parties reviewed only 54 submissions. However, during those first 17 months, the FDA permitted third parties to review only a fraction of the types of devices that are eligible under FDAMA.

The FDA's internal policy, as described in October 1998 and November 1998 guidance documents, permitted third-party review of class II devices only if device-specific guidance or recognized consensus standards existed. According to the FDA, this was to ensure "consistency among different third party reviewers" and to "enhance the timeliness of the agency's review process" once a third party submitted a recommendation.

However, we argued to the FDA that products for which no guidance documents or consensus standards exist—a long list that even includes such products as electronic stethoscopes, medical support stockings, and infrared lamps—are exactly the types of products for which third-party review would be most attractive to manufacturers and most beneficial to the FDA.

As you may know, the FDA publishes guidance documents for use by industry and by the agency's own staff. These guidance documents describe preferred approaches for the processing, content, and evaluation of regulatory submissions and the design, production, manufacturing, and testing of regulated products.

Generally, if the FDA has published a guidance document on a particular product, this means that industry professionals and FDA reviewers already have a good understanding of what it takes to determine a reasonable assurance of the safety or effectiveness of that product. Appropriate premarket submissions for these products theoretically should be simpler for manufacturers to assemble and for FDA staff to review.

However, third-party review holds the greatest value for those products for which the FDA has yet to publish a preferred approach to determining safety or effectiveness. In these cases, organizations in the private sector may have particular scientific expertise that does not reside within the FDA and may be able to make sound recommendations to the FDA much more quickly. The FDA, in turn, could then make more timely decisions on whether to clear or approve the products.

After MDMA made these arguments to the agency, the FDA updated the list of devices eligible for third party review in June of 2000, immediately adding 57 devices for a total of 211. In January 2001, the FDA then published a guidance document to initiate a pilot program that will allow third-party review of any device regulated by CDRH that is not prohibited from such review under FDAMA. This two-year pilot adds another 460 devices to the program, which, combined with the June 2000 expansion, represents more than a 300 percent increase in eligible product types from the program as first "implemented" in 1998.

The latest statistics show that manufacturers are already beginning to take greater advantage of the third-party program. Through the first five months of fiscal year 2001, third parties have reviewed 41 submissions, compared to 47 submissions reviewed by third parties during the entire fiscal year 2000. We suspect that this increase in usage is related to the expansion of the program.

While we appreciate the FDA's eventual expansion of the third-party review program to the limits set forth under FDAMA, we wonder why it took so long, particularly since FDA officials constantly lament an agency-wide lack of resources. From our perspective, if resource constraints are indeed a problem at the FDA, then the agency should have fully implemented the third-party program from the beginning and should be promoting to manufacturers the program's potential for shortening product review times and for alleviating the agency's shortage of resources.

Dispute resolution (Section 404)

Another provision of FDAMA for which the actual implementation is incomplete is Section 404, commonly known as the "dispute resolution" provision. Section 404 of FDAMA directed the FDA to establish "a procedure under which [a sponsor] may request a review" of a "scientific controversy" between the agency and the sponsor of a product if no other appropriate legal or regulatory mechanism exists for resolving the dispute.

The FDA's first response was to publish a direct final rule on June 16, 1998 in response to Section 404 of FDAMA. Under this rule, the FDA would have permitted drug and device manufacturers to request review of scientific controversies by an appropriate advisory committee. However, the FDA ended up withdrawing this rule after our industry and others complained that the rule was not consistent with the intent of FDAMA. As the FDA eventually acknowledged, the rule did not contain critical information, such as the process for selecting members of an advisory committee convened to resolve a dispute, the timeframes for conducting the reviews, the standards for granting or denying a review, and the weight to be given to advisory committee recommendations.

In the end, the FDA chose to allow each of its centers to develop a center-specific approach to implementing dispute resolution. For its part, the Center for Devices and Radiological Health has published a draft guidance document outlining how its dispute resolution process will work and has hired an ombudsman to oversee the workings of a Medical Devices Dispute Resolution Panel, which held its first organizational meeting in October 2000.

We are pleased that CDRH has set up a separate advisory panel and has hired an ombudsman to deal with dispute resolution, and we hope that CDRH and FDA officials will give the panel's decisions due deference. However, the panel has yet to hear its first dispute, though we are aware of companies that have petitioned for a hearing. As a result, it is difficult for us to assess this provision of FDAMA. Once we have had a chance to observe the workings and actions of the Medical Devices Dispute Resolution Panel, we will report back to the subcommittee with our impressions.

"Least burdensome" pathway to market (Section 205)

Implementation of the "least burdensome" provisions of FDAMA is another area of the law for which we would give the FDA an "incomplete" mark. As a result of the FDA's initial unwillingness to work collaboratively with industry on this issue, the agency only two days ago released in draft form its long-awaited guidance document to explain its comprehensive approach to implementing the "least burdensome" provisions. This delay of more than three years since the passage of FDAMA is a critical shortcoming of the agency's implementation efforts, as these provisions capture best the true spirit of FDAMA—ensuring that unnecessary regulatory requirements do not delay patients' access to new technologies.

As you know, FDAMA added the following two provisions, commonly referred to as the "least burdensome" provisions, to the Federal Food, Drug, and Cosmetic Act:

Section 513(a)(3)(D)(ii)

> "Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

Section 513(i)(1)(D)

> "Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."

Industry sought these provisions to remedy one of the major problems we perceive at the FDA: the inconsistent application of law, regulation, and guidance by FDA officials in the review of marketing applications. This inconsistency has contributed to excessive review times that have delayed the introduction of new or improved products. These delays, in turn, have a disproportionate impact on entrepreneurs who are trying to bring their first devices to market, not to mention the patients who are waiting for these innovations.

The FDA held its first public meeting to discuss the "least burdensome" provisions on January 4, 1999, more than a year after President Clinton signed FDAMA into

law. At that meeting, industry representatives offered to work together with the FDA in a joint agency-industry-consumer working group to develop guidance on implementing the "least burdensome" provisions. The FDA verbally rejected our offer during the January 4, 1999 meeting, and the rejection was reiterated in a February 18, 1999 letter to participants at that meeting. Despite the willingness often voiced by FDA officials to work collaboratively with industry on the development of guidance documents, the letter informed us that the FDA had "determined that the time and resource commitment necessary to proceed via that mechanism at this time will be less efficient than building upon the extensive information and varied opinions that have already been expressed on this issue."

Over the course of the ensuing two years, and thanks to the interest and involvement of this subcommittee's members and staff, the FDA relented on its original unwillingness to work with industry on the implementation of the "least burdensome" provisions. To their credit, CDRH officials did accept another offer extended by industry in November 1999 to work collaboratively on developing guidance. Over the next five months, CDRH held a series of meetings with the Least Burdensome Industry Task Force, a working group comprised of representatives from the various national and regional industry associations. The meetings culminated in the agency's March 2000 release of a paper that reflected the spirit of this joint effort, which was to capture the intent of the "least burdensome" provisions and to aid in their incorporation into the device development process.

On May 1, 2001, the FDA finally released a draft guidance document based on the agency-industry paper. This draft guidance correctly notes that FDAMA did not change the standard for premarket clearance or approval of medical devices, and defines "least burdensome" to mean an approach to addressing a premarket issue "that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA." The guidance document also identifies the following basic principles that flow from the "least burdensome" provisions:

- the spirit and the letter of the law should be the basis for all regulatory decisions;
- information unrelated to the regulatory decision should not be part of the decision-making process;
- alternative approaches to all regulatory issues should be considered to optimize the time, effort, and cost of reaching proper resolution of the issue; and
- all reasonable mechanisms to lessen review times and render regulatory decisions within statutory timeframes should be used.

The draft guidance document describes how the "least burdensome" principles should apply to 510(k) submissions and premarket approval applications, and outlines some general applications of the principles.

We are pleased that the FDA published this draft guidance on the "least burdensome" provisions in time for today's hearing, and we trust that the agency will continue to train its reviewers and its advisory panels in the application of these concepts and principles to their responsibilities. While the wording of the recent guidance on the "least burdensome" principles is important, these training activities are just as crucial to promoting the greater consistency we seek in the FDA's review process.

In addition, we hope the FDA is developing metrics with which to gauge whether the "least burdensome" principles are being employed consistently. On this point, we would like to commend CDRH for taking what looks like a step in this direction.

As part of its February 28 final guidance on the "early collaboration meetings" required under Sections 201 and 205 of FDAMA, CDRH published a set of checklists that it will collect from meeting participants. The FDA intends these checklists for use by both the applicant and the agency's review team leader in assessing the FDA's incorporation of the "least burdensome" approach in determining the type of valid scientific evidence needed for marketing approval.

We believe that the FDA should use such checklists or other appropriate tools as part of an ongoing process of measuring the application of the "least burdensome" principles in the day-to-day work of the agency. Without such evaluation, it will be impossible to determine whether the "least burdensome" provisions of FDAMA are being implemented successfully or whether controversies that arise between the agency and manufacturers are isolated difficulties or represent more systemic problems.

NEED FOR CONTINUED MODERNIZATION OF THE FDA

MDMA commends the subcommittee for holding this hearing to see whether the law you wrote is being implemented as you intended, and we encourage you to continue this evaluation. We believe, however, that the modernization of the FDA cannot be achieved fully through just one piece of legislation. The "modernization" of

the FDA should be a continuous process that ensures that the organization and its culture keeps up with and adapts to its environment. The milieu in which the FDA operates is one of constant change and continual advances in medical technology, and we need to ensure that the FDA has the tools and the talent to deal with a world in which the pace of innovation undoubtedly will increase.

I will offer an example to illustrate this point. On the horizon, we see a number of products in development today that blur the traditional lines between devices, pharmaceuticals, and biologics. Stents coated with drugs to fight restenosis and other conditions; implanted drug-delivery pumps; artificial livers, kidneys, and pancreases; nerve regenerators; and devices that deliver genetic therapies are but a few of the "combination products" upon which physicians, engineers, and researchers are working currently. MDMA believes that the regulation of these drug-device and biologic-device combinations presents a variety of challenges for the FDA and, by extension, for the companies that will develop these products.

Congress acknowledged the challenges inherent in regulating combination products in the Safe Medical Devices Act of 1990 (SMDA). Section 16 of SMDA emphasized that the FDA must regulate a combination product based on the product's primary mode of action. In other words, if the FDA determines that a product's primary mode of action is pharmaceutical, then the task of regulating that product falls to the FDA's Center for Drug Evaluation and Research (CDER).

Although a product's primary mode of action determines which FDA center is responsible for its regulation, the designated center often needs additional expertise regarding components of the product that are outside its jurisdiction. In recognition of this, CDRH entered into intercenter agreements in 1991 with CDER and with the FDA's Center for Biologics Evaluation and Research (CBER). The agreements outline how the center with jurisdiction over a combination product may or must consult with the other centers.

When the primary mode of action of a combination product is obvious, the FDA can assign jurisdiction quickly and the review process usually runs smoothly. However, we anticipate that many of the combination products in development today, such as those I mentioned earlier, will be more difficult to categorize and will not fit neatly into the 1991 intercenter agreements. To avoid unnecessary delays in reviewing these products, we need to prevent jurisdictional disputes or inefficient review processes that result from disagreements within the FDA or between the FDA and a manufacturer. The longer the FDA takes debating jurisdiction and regulation, the higher the costs to manufacturers and to patients, since the process of clearing or approving a product for marketing cannot begin until the FDA decides which of its centers has the power to grant the clearance or approval.

The FDA already has begun to recognize these difficulties. To promote consistency in the regulation of cellular and tissue-based products, for example, CBER and CDRH established in 1998 a Tissue Reference Group (TRG) comprised of three representatives from each center. The TRG provides manufacturers of these products with a single reference point for answers to questions regarding jurisdiction, policy, and regulations. The TRG, which meets twice per month, also participates in developing guidance documents in the areas of tissues and cellular therapies.

Congress could build upon such ideas for solving these problems by directing the FDA to establish an Office of Combination Products. Such an office should have the authority to determine how a combination product will be reviewed and to coordinate all involvement by and interaction between the various FDA centers in the review of specific marketing applications. We believe such an office could operate with a very small but multi-disciplinary staff, augmented on an *ad hoc* application- or technology-specific basis by experts on detail from the various FDA centers. Such an office would improve upon the current process of managing the review of combination products, and would also reduce the likelihood that disagreements between centers, which manufacturers cannot control, will delay the review process.

The hybrid products I mentioned earlier are but a few examples of the wave of innovation for which the FDA must prepare itself. As we speak, scientists are investigating how to provide physicians and patients with greater therapeutic feedback by integrating information technologies and wireless communication capabilities into medical devices, engineers are exploring how to use nanotechnological concepts to create tiny medical tools to advance the science of minimally invasive medicine, and researchers are studying how to develop customized therapies based on an individual patient's own genetic or cellular characteristics. These areas of inquiry, as you might imagine, are just the tip of the proverbial iceberg.

Some of these explorations will prove fruitful, and some will not, but all of them will present the FDA with complicated regulatory dilemmas. To help prepare the FDA for the challenges it will face in the new century, the national device industry associations—MDMA, the Advanced Medical Technology Association (AdvaMed),

and the National Electrical Manufacturers Association (NEMA)—are working together to develop a series of legislative proposals for the subcommittee's consideration. The ideas we are developing, such as the one I have outlined, are aimed at enabling the FDA to use its resources more efficiently, augmenting the expertise of the agency's staff, and assuring the FDA's accountability for its actions. We look forward to sharing these ideas with the subcommittee in the near future and to the vigorous debate that we hope to engender about the continued modernization—or, more appropriately, the "futurization"—of the FDA.

Mr. BILIRAKIS. Thank you very much, Mr. Northrup.

Dr. Applebaum?

STATEMENT OF RHONA S. APPLEBAUM

Ms. APPLEBAUM. Thank you, Mr. Chairman, for the opportunity to represent the food industry and give you our perspective on the implementation of FDAMA. The National Food Processors Association is the Nation's largest food trade association and the industry's leader on scientific, technical, and regulatory issues involving food science and food safety. We operate three laboratory centers, including one here in Washington.

NFPA believes that the passage of FDAMA represented a significant advance in the statutory environment to provide responsible information to the public relative to conventional foods. We appreciate this committee's work to address many of the problems in the foods area that our member companies experienced prior to FDAMA, and in particular, we appreciate the efforts of Congressmen Ed Whitfield and Ed Towns, who authored the bulk of the FDAMA food provisions.

In the regulation of foods, FDAMA resulted in: one, the approval of irradiation for use on red meats; two, a streamlined process for approving food contact substances which are primarily used in food packaging; and three, a reduction in label clutter through the elimination of the requirement of a statement referring consumers to nutrition label on food products.

Despite these successes, the Agency's implementation of food labeling reforms for health claims, which provide consumers with important health information about food products as well as irradiation labelling, has been a disappointment. FDA remains reluctant to permit certain types of food labelling that would give consumers important health and safety-related information.

The food labelling provisions of FDAMA were reaction to decades of overly restrictive policies that inhibited truthful and non-misleading label statements. Unfortunately, FDA has taken great pains in its implementation of these provisions to exclude as many claims as possible. FDA turned down the first nine health claims submitted under new FDAMA provisions. Two FDAMA claims were authorized for whole grain foods and heart disease and cancer, and for potassium and reduced risk of hypertension. But these small achievements are not adequate proof that FDA has abandoned its restrictive policies on health claims.

FDA's overly restrictive labeling policies have not withstood judicial scrutiny since FDAMA was enacted. In the key case on health claims, Pearson v. Shalala, the court held that FDA must consider whether appropriate disclosures could render a health claim on dietary supplements truthful and non-misleading even if it was based on preliminary scientific findings. The court also held that FDA's

failure to consider authorizing health claims accompanied by a disclaimer violated the First Amendment.

The holding in the Pearson decision required that FDA revisit its decision on the four contested dietary supplement health claim petitions that were the basis for the complaint. But the case has implications that reach far beyond its facts. Indeed, the Pearson decision called into question the overall regulatory policies used by FDA for authorizing health claims.

On December 1, 1999, FDA announced its plan to implement the Pearson holding. The implementation plan is referred to by the Agency as the 10-year plan because of its estimated decade-long timetable for implementation. With all due respect, NFPA maintains that it is unacceptable for conventional foods to wait until 2010 for relief from restrictive health claims policies.

FDA's labelling policy also discourages important food safety technologies, such as irradiation, from coming to market. In report language accompanying FDAMA, Congress called for amendment of the existing irradiation disclosure regulation, and instructed FDA to explore alternative labeling for irradiated food, noting any required disclosure should not be perceived as a warning or give rise to inappropriate consumer anxiety. Despite this Congressional directive, FDA has been slow to act, only publishing an advanced notice of proposed rulemaking regarding alternative labeling for irradiated products in 1999, with no further action to date. Nevertheless, NFPA is encouraged, but we wonder why this important reform of food safety information is taking so long.

In conclusion, the Pearson decision and FDA's response to it, as well as its reluctance to review its labeling policy for irradiated foods, highlights the facts that FDA historically has approached food labeling restrictively. FDA has been slow to move away from this approach, and generally has done so at the direction of Congress or the judiciary.

Again, we appreciate very much the important reforms this committee made in FDAMA. We stand ready to provide this committee with whatever assistance it may need as it considers the successes and disappointments of FDA's implementation of this important public health law. Thank you very much.

[The prepared statement of Rhona S. Applebaum follows:]

PREPARED STATEMENT OF RHONA S. APPLEBAUM, EXECUTIVE VICE PRESIDENT, SCIENTIFIC AFFAIRS AND REGULATORY AFFAIRS, NATIONAL FOOD PROCESSORS ASSOCIATION

Mr. Chairman, my name is Rhona Applebaum, Executive Vice President for Scientific Affairs of the National Food Processors Association (NFPA). NFPA is the voice of the $460 billion food processing industry on scientific and public policy issues involving food safety, nutrition, technical and regulatory matters and consumer affairs. NFPA's three scientific centers, its scientists and professional staff represent food industry interests on government and regulatory affairs and provide research, technical assistance and consultation, education, communications and crisis management support for the association's U.S. and international members. NFPA members produce processed and packaged fruit, vegetable, and grain products, meat, poultry, and seafood products, snacks, drinks and juices, or provide supplies and services to food manufacturers.

NFPA believes that the passage of the Food and Drug Modernization Act of 1997 (FDAMA) represented a significant advance in the statutory environment to provide responsible information to the public relative to foods. NFPA and its member companies appreciate this Committee's work to address many of the problems in the foods area that our member companies experienced prior to FDAMA. In particular,

we appreciate the efforts of Messrs. Whitfield and Towns, who authored the bulk of the FDAMA food provisions. In the regulation of foods, FDAMA resulted in: (1) the approval of irradiation for use on red meats; (2) a streamlined process for approving food contact substances, which are primarily used in food packaging; and (3) a reduction in label clutter through the elimination of the requirement of a statement referring consumers to the nutrition label on food products (the referral statement).

Despite these successes, the agency's implementation of food labeling reforms for health claims which provide consumers with important health information about food products, as well as irradiation labeling, has been a disappointment. In the hearings that culminated in FDAMA, many Members of this Committee expressed the hope that statutory reforms would, among other things, help change the culture at FDA. Unfortunately, with regard to food labeling, these culture changes have not been realized—FDA remains reluctant to permit certain types of food labeling that would give consumers important health and safety related information. Thus, FDA, though well-intentioned, prevents consumers from receiving truthful, non-misleading information about their foods.

HEALTH & NUTRIET CONTENT CLAIMS

The food labeling provisions of FDAMA were a reaction to decades of overly restrictive policies that were inhibiting truthful and nonmisleading label statements. Despite Congressional attempts to create a workable food labeling policy through the Nutrition Labeling and Education Act of 1990 (NLEA), FDA implemented the NLEA, especially the health and nutrient content claim provisions, in an overly restrictive manner. As a result, Congress, through FDAMA, established alternative pre-market notification procedures for health claims and nutrient content claims which are based on, and consistent with, the published statement of an authoritative U.S. scientific body responsible for public health protection.[1] But FDA has taken great pains in its implementation of these provisions to exclude as many claims as possible. FDA turned down the first nine health claims submitted under this provision.[2] With regard to eight of the nine claims, FDA asserted that they were not based on sufficiently "authoritative" statements.[3] Two FDAMA health claims have been authorized—for whole grain foods and heat disease and cancer, and for potassium and reduced risk of hypertension—but these small achievements do not illustrate that FDA has abandoned its restrictive policies on health claims.

FDA's overly restrictive labeling policies have not withstood judicial scrutiny since FDAMA was enacted. Specifically, in *Pearson v. Shalala,*[4] dietary supplement manufacturers, distributors, and consumer organizations brought suit against FDA, alleging that the agency's regulation of health claims in supplement labeling was an unconstitutional restriction of their First Amendment rights. The court held that FDA's failure to consider authorizing health claims accompanied by a disclaimer violated the First Amendment.[5] The court termed the justification of FDA's restrictions, "almost frivolous."

The supplement manufacturers had unsuccessfully petitioned FDA to approve proposed health claims accompanied by qualifying statements that would disclose any shortcoming regarding the sufficiency of the scientific evidence supporting the claims.[6] Using the First Amendment analysis for commercial speech, which was first articulated in *Central Hudson v. Public Service Com'n of N.Y.,*[7] the court found that, while the FDA had a substantial governmental interest and the challenged regulation directly advanced that interest, there were less restrictive means available to achieve the ends sought.[8] In particular, the court held that—FDA was required to consider whether inclusion of appropriate disclosures would negate the otherwise misleading nature of a health claim such that the claim accompanied by a disclosure could be authorized.[9]

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[1] 21 U.S.C. § 343(r)(3)(C). (This alternative is in addition to the existing mechanism for approval of such claims, found at 21 U.S.C. § 343 (r)(4), which allows persons to petition FDA to issue regulations authorizing the use of a health claim. In order for a health claim to be authorized, FDA must find "significant scientific agreement" that the claim is appropriate).

[2] See 63 Fed. Reg. 34,084 (June 22, 1998).

[3] *Id.*

[4] 164 F.3d 650 (D.C.Cir. 1999).

[5] *Id.* at 658.

[6] *Id.* at 653-54.

[7] 447 U.S. 557 (1980)

[8] *Pearson,* at 657.

[9] *Id.* at 658. ("It is clear, then, that when the government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure misleadingness—government disregards a 'far less restrictive' means.").

In finding that disclosures are preferable to complete suppression of commercial speech, the court did not conclude that all health claims may be made truthful with the use of a disclosure, and deferred to FDA to determine whether a claim is so misleading that it could not be rendered nonmisleading by a disclosure.[10]

The holding in the *Pearson* decision required that the FDA revisit its decision on the four contested dietary supplement health claim petitions that were the basis for the complaint, but the case has implications that reach far beyond its facts. Indeed, the Pearson decision called into question the overall regulatory policies used by FDA for authorizing health claims.

On December 1, 1999, FDA announced its plan to implement the *Pearson* holding. The implementation plan is referred to by the agency as the "Ten Year Plan" because of its estimated decade-long timetable for implementation.[11] The plan is narrowly structured to address health claims for dietary supplements exclusively, reserving for later resolution any possible applicability of the *Pearson* decision to conventional foods, despite the fact that the regulations at issue in *Pearson* apply to both dietary supplements and conventional foods. With respect, NFPA maintains that it is not acceptable for conventional foods to wait until 2010 for relief from restrictive health claim policies.

IRRADIATION LABELING

In addition to preventing consumer access to important health information about their food products, FDA's labeling policy discourages important food safety technologies from coming to market. In the Statement of Managers, which accompanied FDAMA, Congress called for amendment of the existing, highly prescriptive irradiation disclosure regulation. As previously mentioned, irradiation was finally approved for use on red meats after the petition was pending for nearly three and a half years. In addition, irradiation has been approved for use on poultry, shelled eggs, flour, produce including, potatoes and other fruits and vegetables. Yet, we rarely see irradiated foods in our local grocery stores. Why is that? The answer can be found on the food label.

FDA currently requires irradiated products to state that they are "Treated with Radiation" or "Treated by Irradiation" and bear the international symbol for irradiation, known as the radura logo. With the passage of FDAMA Congress required textual disclosure be no more prominent than the ingredient statement on the food product. Although FDA has implemented that FDAMA requirement, it has taken little action to address Congress' directive that the agency conduct a substantive review of its irradiation labeling policy.

As part of the Statement of Managers accompanying FDAMA, the conferees instructed FDA to engage in notice and comment rulemaking to explore alternative labeling for irradiated food products. In their instruction to FDA, they noted, "The conferees intend for any required disclosure to be of a type and character that it would not be perceived to be a warning or give rise to inappropriate consumer anxiety." Despite this Congressional directive and aggressive follow up by the Appropriations Committee, FDA only published an advanced notice of proposed rulemaking regarding alternative labeling for irradiated products in 1999.

If a consumer sees a product containing labeling that looks like a warning they won't buy it. In the case of irradiated foods this is a real problem. Many believe that the radura logo resembles an upside down mushroom cloud. The words "irradiation" and "radiation" are discomforting to consumers—research shows this. By engaging in a notice and comment rulemaking, FDA can use its expertise to create a science-based labeling policy for irradiated foods that makes sense. Although this nation has one of the safest food supplies in the world, incidents of foodborne illness do occur. An important food safety technology like irradiation can go a long way in eliminating the incidence of foodborne illness. FDA's current labeling requirements for irradiated foods do not address statements on food safety benefits and discourage marketing of these foods. In the interest of food safety, FDA must act on irradiation labeling now. NFPA is encouraged that FDA is seeking to undertake consumer research on irradiation labeling, but we wonder why this important reform of food safety information is taking so long.

The *Pearson* decision, and FDA's response to it, as well as its reluctance to review its labeling policy for irradiated foods, bring into sharp focus FDA's disregard of commercial speech protection. FDA historically has approached food labeling restrictively, chilling dissemination of truthful and nonmisleading information and prescriptively compelling label disclosures. FDA has moved away from this approach

[10] *Id.* at 659.

[11] See Dietary Supplement Strategy (Ten Year Plan) (Jan. 2000).

only grudgingly, generally at the direction of Congress or the judiciary. The agency's food labeling regulation today remains constitutionally infirm and suspect in a number of areas.

CONCLUSION

NFPA appreciates the important food reforms this Committee made in FDAMA. We stand ready to provide this Committee whatever assistance it may need as it considers the successes and disappointments of FDA's implementation of this important public health law.

Thank you.

Mr. BILIRAKIS. Thank you very much, Doctor.

The Chair will start the inquiries.

Dr. Suydam, nothing in PDUFA requires FDA to approve a drug application. Correct?

Ms. SUYDAM. That is correct.

Mr. BILIRAKIS. Then the performance goals, as I understand them, merely require the FDA to review and act upon applications. In the written testimony of witnesses in the second panel, and from discussions with the staff too, there have been claims made that PDUFA has lead to the public health and safety being compromised due to increased drug recalls.

Is there any truth to such an assertion? Does the FDA sacrifice the safety and effectiveness requirements because of PDUFA? I assume your answer to that of course would be no, it does not.

But take the time to explain.

Ms. SUYDAM. Thank you, Mr. Chairman. The FDA believes that our standards have been maintained, and that we continue to review and approve or disapprove pharmaceutical products based on the quality of the data submitted to us, and the fact that the data support the product being approved.

I might point out that the rate of withdrawals from the market, which is in fact one way to measure whether in fact safety has been in any way inhibited, is the same as it has been for the last 20 years. The rate is somewhere around 2.9 percent. That has been the case for 20 years. Now the number might be higher because we are approving more things. More things are on the market than were on previously. But the rate of withdrawals has remained steady for approximately the last 20 years.

Mr. BILIRAKIS. This is a very significant claim on their part. I think that all parties would agree that the modernization act has worked well, that PDUFA has done what it was intended to do in general. But, there are groups that find fault with it.

Why would they make this claim? There has to be some substance to it, I would think, rather than just all supposition or speculation.

Ms. SUYDAM. There have been some, and my speculation is that there have been some very high profile drug withdrawals in the last few years that have received a lot of public scrutiny and public press. We understand the current concerns of groups about products coming on the market.

I think one thing I pointed out in my testimony that I'd like to reiterate is the fact that the United States is now the country of first introduction for new drugs in 80 percent of the cases. That's very different than it was in the early 1990's prior to PDUFA. So you are more likely or you may be more likely to have a with-

drawal early in the process because of the fact that it's been introduced into a larger population of patients as opposed to the numbers. As a result, you will see the very rare side effects that you might not see during the clinical trials.

Mr. BILIRAKIS. A frequent criticism of PDUFA is that the appropriations thresholds in the statute effectively force scarce dollars into drug reviews at the expense of other important FDA initiatives. Can you respond to that?

Ms. SUYDAM. The FDA budget is obviously restricted, as all Federal budgets are to some extent. I believe that the benefits of PDUFA have really out-weighed the potential costs of moving money from one program to another.

Mr. BILIRAKIS. Has PDUFA been an unanticipated burden on FDA? In other words, from the accountability standpoint?

Ms. SUYDAM. I believe that in my written testimony you will see that the performance goals that have been established under the PDUFA II program, have given us an added burden that I'm not sure warrant the cost of tracking them. For example, we are tracking every meeting with industry. We are tracking the time between when the meeting is set up and when the meeting is held. There are more than 3,500 different entities that have been tracked in PDUFA II.

I think since we have virtually met every performance goal, perhaps now is the time to think about those goals and think about whether we need to have that level of tracking.

Mr. BILIRAKIS. All right. When we finish up here, I would ask you all not only to respond to written questions, but to submit any suggestions to us. Mr. Burr is still here. It's important in the process of reauthorizing PDUFA whenever we do it, that we kind of hear your inputs in terms of suggested changes, legislative changes that we could make which would not hurt the effort but basically benefit, and your help. Thank you.

Mr. Brown?

Mr. BROWN. Mr. Chairman.

First, Mr. Northrup, I want to compliment you on your testimony. I agree with you that obviously FDA modernization is a continuous process. It seems to me that the variety of products in the device field surpasses that of any other area of FDA oversight and regulation. That invites new challenges for keeping FDA both responsive and responsible. I was intrigued by your proposal for a new Office of Combination Products and look forward to learning more about the details as that unfolds from you.

Dr. Suydam, I was intrigued by your comments on page 10, that 80 percent of new drugs worldwide first launched in the U.S. was 40 percent before this legislation. You used the words, "due to the favorable regulatory climate." I would like to know on what information you base that. Also, could the reason be, I mean I understand that the numbers are easily provable, but whether it's due to the regulatory climate, I would also think it might be in part due to the fact that when products are launched in the United States, the economic gain is potentially greater because this Congress has done little—some think it shouldn't and some think it should—this Congress has done little of any kind of changing the price structure. No other country allows prescription drug prices so

freely to move, if you will, that prices are higher here than in other countries in the world.

Is that also a major reason that this huge increase in the number of drugs launched in this country has occurred?

Ms. SUYDAM. Mr. Brown, it could very well be that that's part of the reason. But what I was focusing on was the fact that under FDAMA with the increased resources provided for us under PDUFA, we have reduced the median review times from 20 months down to 12 months for normal product applications, and from 12 months to 6 months for priority applications. I think that in itself speaks to one of the major reasons why we are the country of first introduction for new pharmaceuticals.

Mr. BROWN. You would say that's, in your mind, that's clearly the primary reason for the increase, not the fact that prices are significantly higher here and the reward significantly higher here economically for the launch of those new products?

Ms. SUYDAM. I think that's probably one of the other reasons, but FDA's purview is not necessarily to look at the economics of the industry in that sense.

Mr. BROWN. Except you made a statement here, "due to the favorable regulatory climate," so I would hope that FDA's purview is to come here and if you make an assertion to be able to defend it.

Ms. SUYDAM. Yes. I do believe that we have improved the climate. I think I was making the cause and effect between the times of approval and all of the things that we have done through the implementation of PDUFA, and the change that we've seen in the regulatory review time, and in fact, the whole clinical drug development time in general is down.

Mr. BROWN. I applaud what you have done that way. Does that then beg the issue of responsibility of our government, a responsibility to our citizens and a responsibility perhaps for the introduction of these new drugs that make their way around the rest of the world, that we should put significantly more resources into post-market surveillance? I mean we have seen, if in fact twice as many, percentage-wise, I don't know the raw numbers, but twice as many percentage-wise numbers of drugs have been approved by FDA, meaning there are many more of them on the market, more quickly with a shorter period of time of approval, not less efficient or less safe perhaps, but there are more on the market, more quickly, coupled with direct to consumer advertising, which really had not kicked in with any appreciable degree at the time of FDAMA's enactment, let alone PDUFA's, but FDAMA's enactment. Does that mean that the drug industry and this Congress and the FDA have a significantly greater responsibility in post-market surveillance with the onslaught of new drugs, with the faster approval process, with the direct to consumer advertising, with the more and more people using these drugs much more quickly in much higher numbers than they were ever used before when there weren't these TV ads and the accelerated numbers of visits by people to the doctors, drug reps to the doctors and all that. Doesn't that give us a greater responsibility on post-market surveillance?

Ms. SUYDAM. I believe that it does. In fact, the Agency's budget last year included some additional money for adverse event reporting systems and also this year's proposed budget, the 2002 budget,

includes dollars to enhance those efforts across all of our product areas, because we do believe that we really need to focus on post-market as well as the pre-approval side of our whole regulatory responsibility.

Mr. BROWN. Have we come close to, not in terms of equalizing in dollars for sure or even employees, but have we come close to meeting our responsibilities in the post-market surveillance in comparison to meeting our responsibilities on the clearance, on the drug approval?

Ms. SUYDAM. Well, I think our budget proposals would lead one to the conclusion that we need additional resources to enhance our post-market study of products.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. BROWN. Can I ask for a more specific answer? I'm sorry, Mr. Chairman.

Mr. BILIRAKIS. Very brief.

Mr. BROWN. Have we done as well with our responsibility in post-market surveillance as we have in this Congress and the FDA in carrying out its responsibility to accelerate the approval process?

Ms. SUYDAM. I think, Mr. Brown, that the PDUFA program itself has focused on pre-market, and therefore, the resources have been added to that program.

Mr. BROWN. I'm not talking about that. I am talking about the responsibility to the public. Have we done as well in post-market surveillance as we have on speeding the approval of drugs to the market?

Ms. SUYDAM. I think it is hard to make the judgment that we have done as well. I think we have done the very best possible job we could do with the resources we have available to do it.

Mr. BROWN. That really isn't my question, but I am not going to get the answers.

Mr. BILIRAKIS. Mr. Greenwood, to inquire?

Mr. GREENWOOD. Thank you, Mr. Chairman.

I am going to address my questions to you, Dr. Suydam, and on pediatric exclusivity. As I alluded to in my opening comments, I don't think there is any question about the fact that this provision has been an enormous success. Some of the numbers, 11 pediatric studies done between 1991 and 1996, 411 studies done since 1998. Estimates of lower hospitalization costs due to better pediatric dosing information can save up to $228 million per year for five diseases alone.

President Clinton's FDA report said that "pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date." I could go on with all of this. This estimate that if we could reduce even one-one-hundredth of the annual economic impacts from these leading causes of death and disability by providing more effective treatments to children, making for healthier adults in the process, the $7 billion saved each year would be 10 times more than the nearly $700 million that FDA has estimated is the yearly cost to society from the pediatric exclusivity awards. That's from the Tufts study. So that it has been a success is not a question.

What the question obviously is is, is the 6 months the right number? Does it lead to what some have called windfall profits and so forth? The only ways I can think of to change that is to change if people think that some drug companies make too much money is to reduce the 6 months for everybody or have some sliding scale negotiated, additional exclusivity that would be negotiated between the companies and the FDA. I worry about that because it puts a whole lot of uncertainty into the process. At least what we have now is certainty.

I am interested in your thoughts about this. Do you have concerns about the 6 month exclusivity? Do you think we should tamper with it?

Ms. SUYDAM. Mr. Greenwood, the Administration really has not had an opportunity to fully discuss the entire pediatric exclusivity provisions. We really have not come to any positions on the 6 month exclusivity at this time. But we will be happy to work with the committee in the future on both the pros and cons of the 6 months.

Mr. GREENWOOD. Let me ask this. The FDA has requested—can you tell me how many studies have been initiated by the FDA?

Ms. SUYDAM. We have issued 188 written requests for pediatric studies.

Mr. GREENWOOD. Okay. Has it been your experience that companies have declined studies because of lack of financial incentive?

Ms. SUYDAM. I don't believe that that has been the case.

Mr. GREENWOOD. Did FDA have any expectations prior to the passage of the pediatric exclusivity provisions about what to expect, the number of requests that it would generate? If so, have the number of requests exceeded your expectations?

Ms. SUYDAM. Obviously the response from the pharmaceutical industry has been incredibly vigorous. We have wanted to have this kind of activity for many years, and have not been successful prior to the passage of this particular provision in getting the pediatric studies done that we thought were necessary.

Mr. GREENWOOD. Let's turn to the issue of whether you need more resources on the generic side of the house. Are you able to comment about that?

Ms. SUYDAM. Our generic program is a program that I think has a tremendous workload. We have approximately 300 FTEs—people—in that program in general. We are not meeting the statutory review times that have been laid out for us in the law.

Mr. GREENWOOD. Do you have estimates of what it would take to get up to the statutory review time?

Ms. SUYDAM. I do not. But we would be glad to explore that and get back to you.

Mr. GREENWOOD. Would it be fair to say it's on the order of magnitude of something like 10, 15 to 20 pediatricians? I'm sorry, not pediatricians, excuse me, additional staff members. Is that the ballpark?

Ms. SUYDAM. I really have not looked at the issue of how much it would take to meet the deadline. So I think I would prefer not to answer in specifics.

Mr. GREENWOOD. Thank you. My time has expired.

Mr. BILIRAKIS. Mr. Pallone, to inquire?

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask Dr. Suydam, I mentioned in my opening statement about with regard to pediatric exclusivity, that the FDA's interpretation of the law has in my opinion in essence has been granting companies patent extensions without receiving the pediatric benefits it was intended to generate. That was my concern.

Two areas I mentioned was the ability of companies to use old studies to obtain patent extensions, and the granting of exclusivity based on active—I guess that's moiety—I don't know if I'm pronouncing it right.

Ms. SUYDAM. Moiety, yes.

Mr. PALLONE. Rather than on a product-by-product basis. So what I hear is that they are using old studies, and they are not necessarily relevant product-by-product. What do you think about that? Should we be prospective in the way we look at this? Should the law be changed in that respect? I just wanted your comment on it.

Ms. SUYDAM. Mr. Pallone, I think the most important thing about the pediatric exclusivity provision is that studies are being done. Studies are being done for the first time. We are getting products labelled, which is the actual outcome you want, so that physicians everywhere know how to use a product and how to use a product correctly. So I think in general it has been a very positive program. I don't think that there has been a lot of the things that you have mentioned.

Mr. PALLONE. You're not concerned that it goes against the intent or somehow it's not in accordance with the intent?

Ms. SUYDAM. I believe the intent of the act was to have products labelled so that physicians everywhere in the United States can understand the effect of that particular product for their patients of all ages. I think that intent is being met.

Mr. PALLONE. I mentioned also dietary supplements. I wanted to ask you a question about that. The industry and the public have been asking for these proposed final regulations for good manufacturing practices. They haven't been published yet. I was wondering if you could tell us when they are likely to be published? It seems like it has taken them more than 6 years to get these quality standard regulations for dietary supplements. I would just like to know what we can do in Congress to assist the Agency to do a better job in this, because I think it is a major problem that these haven't come out.

Ms. SUYDAM. We agree with you, Mr. Pallone, that good manufacturing practice regulations for dietary supplements are essential. They are a high priority for the Agency. The regulation is now under review by the Administration. We hope that it—the proposal, will—it's a very complex regulation—not something that is easy to review—be available shortly.

Mr. PALLONE. You don't have an idea of the date though, this summer, fall?

Ms. SUYDAM. No. I'm sorry, I don't think I can.

Mr. PALLONE. All right. Let me ask one more thing. That is, this is with regard to medical devices. I know you have the 510(k) reviews, devices that already exist like a pacemaker, and you have the PMA reviews for new devices. The 510(k) reviews are close to

meeting the statutory requirements of FDAMA, but the PMA review has taken a lot longer. Of course the whole purpose of FDAMA primarily I think was to address these breakthrough products. These are the ones that can bring tremendous improvements to the lives of patients.

So I was wondering what combination of resources, whether it be appropriations, legislation or whatever, would be necessary to achieve statutory compliance for the PMA reviews as well as the 510? But there's obviously a big difference now in terms of the time.

Ms. SUYDAM. Mr. Pallone, the timeframe for 510(k)s has been 90 days that is the statutory deadline. Surprisingly a large number of products come through the 510(k) process. Even some relatively new or what might be considered somewhat novel products, more than 4,000 were approved last year through the 510(k) process. So it is a significant workload. I think companies are particularly pleased that our performance there is good.

I agree that we need to work on enhancing our pre-market approval in the area of medical devices for those complex devices. But I would point out that these are far more complex products. You have far more information to review. We do need additional time to look at those products. So it could be a combination of additional resources, and also making improvements in the process itself. The times have come down significantly since where they were in 1995.

Mr. BILIRAKIS. The gentleman's time has expired.

I didn't mean to interrupt your response.

Mr. Whitfield?

Mr. WHITFIELD. Thank you, Mr. Chairman.

Dr. Suydam, the food labelling provisions that we included in FDAMA were adopted specifically in reaction to what we considered decades of overly restrictive policies inhibiting truthful and non-misleading label statements. As you are aware, we specifically provided for pre-market notification procedure for health claims, content claims which were based on, consistent with, published authoritative, scientific bodies on that issue.

So after FDAMA was enacted, the first nine claims, health claims were turned down, denied by FDA. A lawsuit was brought, in Pearson v. Shalala case. The court ruled that FDA's restrictions were unconstitutional basically or a violation of free speech. They specifically said that the restrictions were almost frivolous, and remanded it back to FDA. It is my understanding that now FDA has adopted a 10-year plan to review this as it applies to dietary supplements. Even though the regulations at issue in Pearson v. Shalala included not only dietary supplements but also the conventional food plan. You all even wrote a letter to a Member of Congress saying we're not going to apply this food plan unless the court specifically orders it.

Now it appears to me as a member that was involved in that part, that you all almost defied the intent of Congress in making it easier to get these claims labels out there on not only health supplements, dietary supplements, but also food, conventional food.

Ms. SUYDAM. Mr. Whitfield, clearly it is not the Agency's position to willfully ignore the intent of Congress on this particular provision. I would like to point out that after our guidance was issued

on health claims, the two claims that have been submitted since then were approved. We think that the guidance document in itself will provide the kinds of information that people need to do in order to have a health claim approved.

We agree with you that valid information needs to be on the label, and the label is an incredibly important document. We need to assure that it is accurate and not misleading. I mean that's clearly important, incredibly important to us.

I want to point out that the 10 year plan is an overall plan, a strategic plan for dietary supplements in general. I would not construe it to be that we aren't going to move on health claims for conventional foods until after we have finished all of the 10 year activity on dietary supplements. I think it was designed to look at the entire category of dietary supplement products and determine all of the activities that needed to be done, and then to put a framework on it, on how can we do this work given the resources we have to implement this program.

Mr. WHITFIELD. Well, the fact that you all wrote this letter to a Member of Congress stating that you did not intend to apply it except if the court specifically ordered it seems a little bit at variance with what you are saying.

I would simply say to you that I don't know who the new head of FDA is going to be. I don't know if you are going to be there or not, but many members of this committee are going to be writing a letter to whoever the new head is, and telling that person that we are going to be looking at this issue closely because as I said in the beginning, I feel like the intent of Congress has not been complied with, and even the court said that they thought the restrictions were frivolous. So I wanted to raise that issue.

Ms. SUYDAM. Thank you, Mr. Whitfield. We will go back and look at that issue.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Deutsch?

Mr. DEUTSCH. Thank you, Mr. Chairman.

Dr. Suydam, I think that—your staff has hopefully briefed you of some questions that I am going to ask regarding the issues regarding Andrex Pharmaceutics and Bioville and the patent issues related to that. I bring them up in this setting for a couple of reasons. One of which is I think all of us understand that the incentives to extend the exclusivity is incredible. I mean the dollar amounts are not in the millions, but in the billions. Very creative, very well-paid attorneys, consultants have come up with just about every possible thing that we can't possibly think of beforehand to try to extend these patents in ways that I think is obviously contrary to the intent of Congress in terms of public policy issues.

As I am sure you are aware at this point, I think this is an issue of first impression, the case of Andrx and Biovail with Tiazac, where there was an exclusivity based on a patent that is almost 17 years old, where a company comes in and basically puts another patent based on the formulary of that drug in a non-approved drug. So it's a drug that hasn't gone through any trials at all. In that case, the FDA listed that patent, so effectively has now extended the exclusivity for 17 additional years. Really almost gaming, I mean the system has been gamed to the detriment of Congres-

sional intent, to the detriment of consumers, to the detriment of basically the entire system.

I know it's a box that you are in. But I guess my question to you is can you get out of the box or do you need Congressional legislation to get out of the box?

Ms. SUYDAM. Mr. Deutsch, I don't have the specifics of those two cases that you cite. I would suggest that we discuss that with you at some other time when we have the specifics.

I would say that I believe the chairman had said he was interested in having a hearing about generics at sometime in the future. I am not prepared to talk about the generic program in that sense today.

Mr. DEUTSCH. Again, I heard the chairman as well. Again, I know my staff has spoken to your staff so I just assumed that you would be prepared maybe more extensively than your last response. This has been going on now for several months.

What I would hope is that I can get a specific response within a relatively short timeframe. This has been going on now literally for several months, so hopefully within a week or so. And that in the response, I don't get—again, I understand the FDA is in a difficult situation, but we are where we are. Do we expect that—I mean what my fear is clearly on the policy side, you know, is once the system has been gamed this way one time successfully, what is to stop every one from gaming the system this way tomorrow, the next day, the next day, the next day? I mean and again, it has been game. I don't think there's anything about that.

So I mean what I'm asking for you is again, the chairman, I am well aware of the hearings that he's talking about. He doesn't have dates for those hearings at this point in time, so let me just ask you point blank. Can I expect a response within a week's period of time?

Ms. SUYDAM. I understand your concerns about the program in general. We will attempt to get you the response you ask for as quickly as possible.

Mr. DEUTSCH. I mean I'm really asking you to commit yourself to a time period, not as quickly as possible. What is the timeframe that you believe you can get back to me on it?

Ms. SUYDAM. Within the next 2 weeks.

Mr. DEUTSCH. Okay. I appreciate that.

Let me also, let me just jump because I see my time is running out. The FDA estimates the 6 month extension for pediatric exclusivity costs the American taxpayer $695 million a year. Could FDA or NIH provide grants to pay for additional pediatric studies? This would seem to be a big savings in comparison to the current system where the NDA holder requests to study and reapplies a significant—you know, reaps a significant reward. The government should focus on the drugs they find important to study and save the taxpayers a significant amount of money.

What criteria is the FDA using to determine if a drug is eligible for pediatric exclusivity at this point?

Ms. SUYDAM. I believe we are following the intent of the statute to determine if there is a use of the product in children, if the product is a legitimate product for use in children.

Mr. DEUTSCH. Is that the extent of the criteria that you are using at this point?

Ms. SUYDAM. I would like to ask Ms. Axelrod to look it up for me in the statute.

Mr. DEUTSCH. I appreciate that.

Mr. BILIRAKIS. The gentleman's time has expired, but I think we should allow a response.

Ms. SUYDAM. We can provide that.

Mr. BILIRAKIS. Maybe a quick response now, then possibly maybe follow it up.

Ms. SUYDAM. Follow it up.

Mr. BILIRAKIS. With something more detailed in writing to Mr. Deutsch and to the committee.

Mr. DEUTSCH. Thank you.

Mr. BILIRAKIS. Can we get a quick response?

Mr. DEUTSCH. If she can't do it now, we can get it back in writing.

Ms. SUYDAM. Okay. I prefer to do that.

Mr. BILIRAKIS. All right. Why don't you do that. If you would please, I would appreciate it.

Let's see, Mr. Upton?

Mr. UPTON. I'm actually not quite ready.

Mr. BILIRAKIS. Not quite ready? That's the first time I have heard that one.

Mr. UPTON. I didn't think I was next in the queue.

Mr. BILIRAKIS. Mr. Burr?

Mr. BURR. Thank you, Mr. Chairman.

Mr. BILIRAKIS. I'm trying to go according to the committee rules, but you guys won't let me.

Mr. BURR. Dr. Suydam, won't you be glad when there is a permanent commissioner?

Ms. SUYDAM. Yes, I will.

Mr. BURR. Let me clarify something for Mr. Deutsch. If it's a drug for breast cancer, are we going to conduct trials on it for pediatric exclusivity?

Ms. SUYDAM. No, I don't believe.

Mr. BURR. How about prostate cancer?

Ms. SUYDAM. I don't believe we would.

Mr. BURR. The majority of the drugs that are coming through applications today actually are targeted for an elderly population. Isn't it true that just a small percentage of those may have some hope to be used in pediatrics? Therefore, a majority of what applications are in the system today would never be considered by the FDA, who ultimately decides each drug that may go through a pediatric exclusivity trial. Right?

Ms. SUYDAM. Yes, that's correct.

Mr. BURR. So in fact, we can look at the FDA not at the industry and say the industry is gaming the system. If there is any mistake that's made, it is where we have evaluated something that we thought would be beneficial to children, and then maybe in the end we found out it wasn't.

Ms. SUYDAM. Right. Or maybe detrimental to children.

Mr. BURR. Yes. We're not going to be perfect, are we?

Ms. SUYDAM. That's right.

Mr. BURR. Isn't the majority of the emphasis behind pediatric exclusivity to make sure that drugs that we were currently giving children that may have potentially done damage? Because we didn't know as much about dosages. We didn't know as much about reactions. Isn't it in fact the pediatricians who have said we have learned some valuable information in the short time that this exclusivity has been offered?

Ms. SUYDAM. Yes. I think you will be hearing later in the second panel from the pediatricians. They will be saying those same things.

Mr. BURR. Let me ask you, should we reauthorize PDUFA now, the user fees?

Ms. SUYDAM. Yes, I believe PDUFA should be reauthorized.

Mr. BURR. No hesitancy on the part of the FDA to do that?

Ms. SUYDAM. No. No, there's no hesitancy on my part.

Mr. BURR. Let me ask you, I'm going to try to clear up a few things that were asked earlier. Is it reasonable for everybody to expect that when you move from a controlled trial of 1,000 people and you have a drug that's approved and it goes to a population of 100,000 people, that we expect we will see some reactions that we didn't pick up in the thousand person controlled trial?

Ms. SUYDAM. Yes. Very reasonable.

Mr. BURR. So what we have gone through since the passage of FDAMA, where all of a sudden people have highlighted new reactions to specific drugs, is not significantly different from what we saw before. Whether the process took 3 years longer if your trial was 1,000 people and it was controlled and it took 3 years longer, we would have never seen those unanticipated reactions until we got to a larger sampling, which in that case would be the patient population.

Ms. SUYDAM. That is correct.

Mr. BURR. Is the FDA concerned about post-approval review?

Ms. SUYDAM. We are concerned about post-approval review, which is one of the reasons we focused our budget in budget requests for the last 2 years, additional resources for us to look at adverse events that are occurring with all products that we regulate.

Mr. BURR. Can I volunteer this subcommittee or certain members on both sides of the aisle to work with the FDA to come up with what all of us can agree is a successful post-approval process?

I think what we currently have at the FDA is deficient. I think that opinion is shared by a number of members on this subcommittee. I believe that with what we have learned and what we know today, we can come up with a mechanism that has the highest degree of confidence that not only that we're watching after we have approved it. In fact we catch things. I don't think the system in fact is that reliant today.

Let me move to Mr. Northrup. The numbers that I have on the 510(k)s is that the average reviewing time is 77 days. Let me just ask you for a clarification. If the FDA is reviewing a 510(k) and they ask for additional information once, twice, 15 times, don't they actually stop the clock, wait until the information is received, and once the information is received, disseminate it, start the clock

back up until the next time they need information, stop the clock? Is that the correct procedure?

Mr. NORTHRUP. That I correct, I believe. I welcome a correction from the FDA if I'm wrong, but I believe that is correct.

Mr. BURR. A 77 day average is in fact a correct time relative to the clock running, but it's not necessarily indicative of the entire length of time that it takes to review.

Mr. NORTHRUP. No, that's true. That time does not include the time that the company is taking in between the time the clock stops and starts to collect the information, submit that to the FDA.

Mr. BURR. How successful have we been, in your opinion, on third party review?

Mr. NORTHRUP. I don't think we have been as successful as we could have been. I think it's true that manufacturers have not taken advantage of third party review, but a large part of that is because the third party review program, until very recently, had not been expanded by the Agency to include all those products that were eligible under FDAMA.

In January of this year, the FDA did in fact release guidance that expanded the program to include all those products that are eligible under FDAMA. So again, I would give them a grade of incomplete. I think it is too early to tell the ultimate success of third party, but we're certainly seeing the numbers start to increase now that more products have been made eligible for the program. We think it will be a success. We hope it will be a success.

Mr. Chairman, I thank you for the time. I yield back.

Mr. BILIRAKIS. Ms. Capps?

Ms. CAPPS. Thank you. I was not a Member of Congress when FDAMA was enacted, but I have heard nothing but praise about the process. I want to commend this committee—because FDAMA came out of this committee and also the FDA—for the landmark progress that you have made in this regard.

But, Mr. Chairman, I am struck by the remarkable nature of this hearing. It may suggest, at least it does enter my mind, that we have in place a regulating agency which, because of tremendous advances in different kinds of advances in technology, the mechanism for regulation is—I guess the word would be archaic. The principles are there, but the changes have been perhaps too dramatic that the regulatory mechanisms don't fit the mold.

I wanted to talk about, I think we had examples from both Dr. Applebaum and Mr. Northrup, areas that are pushing at the limits of what the FDA is capable really of doing. Again, I think it is our responsibility to take this seriously, which is why I think this is so important.

Mr. Northrup suggested that, and my question is to you, Dr. Suydam, that the combination, Office of Combination Products might be established. He listed the example of the stent where it is a device and also a medication. I wanted to know what your reaction is to this suggestion. But I also wanted to explore what the previous questioner sort of just generally brought up in the area of third party review or basically peer review, because I think that's what this is leading toward.

Ms. SUYDAM. Let me answer the last part of the question first.

Ms. CAPPS. The last part wasn't a question yet.

Ms. SUYDAM. Oh okay. All right.

Ms. CAPPS. I'd like you to answer the first part first.

Ms. SUYDAM. I don't think we have had time to evaluate the idea of an Office of Combination Products, although I think it is a very intriguing suggestion. I do know that we have been dealing with combination products for quite some time.

Ms. CAPPS. Yes.

Ms. SUYDAM. We have a mechanism in place where we work with the two parts of FDA to assure that there is a lead center, and that lead center then has responsibility for the overall application, and then works with the other center to make sure that the issues related to the particulars of their product regulations are being met.

I think right now I would not say that that has failed us. I think it has in fact been fairly successful. I think we will have to look at it as we deal with more and more of these products. I, for one, just from a bureaucratic philosophy, don't like the idea of creating new offices because sometimes I think we can use the structure we have in a creative way. That is what I would prefer to do.

Ms. CAPPS. I guess I would suggest that it is so time consuming to make old patterns fit new techniques. Perhaps we could be able to help you. I would like to offer that this is a topic for this committee to really address, whether there needs to be a sense of urgency about it. I know some of these devices are approved for use in other countries. I have a feeling that there are places in this world where lives are enhanced and maybe saved. We're really not where we should be.

That leads me to ask you, I understand Mr. Northrup answered the previous question about third party reviews by saying there has not been time to evaluate it. Well, they didn't get put into place very quickly either. Again, this is kind of breaking the mold of the traditional way of dealing with it. I want to know what again, we can do to assist? Certainly if these techniques and technologies are so innovative, it would be a challenge for FDA to stay in the position of being able to review them. That, I would imagine, is why the idea comes up.

What can we do to legitimize that, to help that to work more efficiently?

Ms. SUYDAM. FDA is very open to the idea of third party review. We believe that the provision is working well and is an idea that is working well.

We were reluctant to start out with a huge number of products in the process initially. I think that is certainly an approach where we chose to be a little conservative and to try to get some experience with the third parties. We did not know what kind of reviews we would be getting from the third parties, how much work it would require on our part once they were finished. Now we have had that experience. We know that there are third parties that are very reputable, that do a good job, that we can use. I think therefore our philosophy was to extend it to the full range of products that were eligible in January, which we did. We will continue to hope that the industry uses it at a greater rate than they have in the past.

I do want to point out that our track record in devices for novel therapies is a good one. Eighty-five percent of the pre-market ap-

proval applications are reviewed in our statutory time. So the outliers are just in that 15 percent.

Ms. CAPPS. I guess I would respond and in closing, I know I have used too much time, by saying that we should get over the fact these are novel. I think this is the future of medicine. Somehow FDA—this is a stretch, but we also need to be able to embrace that this is medical practice today. These areas of combinations of what——

Ms. SUYDAM. Absolutely, we agree with you. We are well aware that that is the case.

Ms. CAPPS. Thank you.

Mr. GREENWOOD [presiding]. Is the gentleman, Mr. Upton, ready?

Mr. UPTON. I'm ready.

Mr. GREENWOOD. The gentleman is recognized for 5 minutes.

Mr. UPTON. Although I'm late for the lunch that you are chairing.

Ms. Suydam, as you know, I introduced legislation that was incorporated into FDAMA back in 1997. It allowed the food manufacturers to put health claims on their labels when the claims are based on authoritative statements by NIH, CDC, and other Federal scientific organizations provided that you all are given 120 day notice.

What I'm interested in today is to take a little snapshot in terms of how that has worked. I think in your testimony, I regret that I was in an Education markup, I think along the lines of about nine notifications have come your way, but I would be interested to know of those, how many have you received? Of those, how many have you turned down, and the reasons for such. How long does it take on average for the FDA to act on those petitions once they are submitted under the pre-approval process? Perhaps what constructive ideas might you offer in terms of how we can even better streamline this process as we look to the days ahead?

Ms. SUYDAM. The record on our health claim notifications is one that I spoke to in that we have received 11.

Mr. UPTON. Denied two?

Ms. SUYDAM. We approved two and denied nine. The two approved had been approved after our guidance was issued, which we believe has helped the process, and will encourage more claims to be approved.

We have been on time for the most part. The 120 day statutory deadline has been exceeded, but I believe we had authority to negotiate with the submitter on an extension which was done, and we met those deadlines at that time.

Mr. UPTON. Do you have any suggestions in terms of what we might do in the future? Or do you think the process is working fairly well?

Ms. SUYDAM. My suggestion is that the guidance document has helped the process. I would like to go back and talk with our people in the Center for Food Safety to ask them to look at the process and see what kind of suggestions we can make to you.

Mr. UPTON. Great. Thank you.

I yield back my time.

Mr. GREENWOOD. The Chair thanks the gentleman, and recognizes the gentleman Mr. Stupak for 5 minutes.

Mr. STUPAK. Thank you.

Doctor, before PDUFA and before you had the drug user fees, how long did it take to approve a drug?

Ms. SUYDAM. For standard applications it took about 30 months.

Mr. STUPAK. Thirty months? Okay, and now under FDAMA, in 1994 according to your testimony, it's down to 20 months, in 1999, about 11.6 months, and you anticipate it could be less than 10 months soon.

Ms. SUYDAM. Yes.

Mr. STUPAK. Okay. So if a drug was approved before FDAMA, less than a year, that was unusual?

Ms. SUYDAM. Yes.

Mr. STUPAK. In the testimony, you indicate that the drug review time has decreased significantly by 22 percent, and under FDAMA II, further review time by the Agency has been reduced. So in some of the answers to the Chair's questions about recent recalls, you said that the FDA has not compromised safety or effectiveness of the drugs, but the percentage of recall is basically the same prior to FDAMA. That is because we have more drugs out on the market. More drugs, we have decreased drug development time, and less review time.

The mistakes and the errors, if you will, or the recalls, we have had what, 11 in the last 3½ years, recalled drugs, that resulted in about 1,000 deaths?

Ms. SUYDAM. I do not know the number exactly. But I am assuming you have the correct figures.

Mr. STUPAK. Sure. Those recalls of at least 11 over the last 3½ years resulting in about 1,000 deaths, and GAO estimates, because it's a voluntary reporting process, your errors, the adverse event reporting system, it's probably 1 to 10 percent, somewhere there, of the actual number. Correct?

Ms. SUYDAM. In overall adverse event reporting, yes. I think probably if you are talking specifically about deaths, it is more likely that we would have those reported.

Mr. STUPAK. Really? Okay. It's still voluntary, right?

Ms. SUYDAM. Yes.

Mr. STUPAK. And a doctor has to make a connection or the manufacturer has to make a connection between the drug and the death before they are required to make the report on the errors?

Ms. SUYDAM. Yes. That is correct.

Mr. STUPAK. Well, see under FDAMA and all these other, the Modernization Act, if it's better, why do we have more deaths than before? I mean take a look at this. Before we went in, in 26 years before FDAMA, you had eight recalls. In 26 years you had eight recalls. In the last 3½ years, you have had 11 recalls. If this is supposed to be better, why do we have more recalls and more deaths than you did in the 26 previous years?

Ms. SUYDAM. Mr. Stupak, I do not have the numbers in front of me to debate your numbers. They don't seem right to me. What I would say is that there have been thousands, in fact probably hundreds of thousands of patients who have been helped because they have had greater access to therapies. They have had that access to

therapies much faster. Therefore, perhaps there are thousands of people who did not die because they had the therapy that they needed.

Mr. STUPAK. That's because we have more drugs out there. Right?

Ms. SUYDAM. Because we have products that provide the benefits that are needed for the patients who have these life-threatening diseases.

Mr. STUPAK. To some of us, that's like saying you know before FDAMA, we had ten airlines and one out of ten would crash. Now with FDAMA, we have 100 airlines, and now we have ten crashes. It's better because we have more legroom, we have better food, ticket price is lower.

You see, some of us feel that if it's supposed to be an improvement, but your percentage of error is the same and the percentage of deaths over people who take prescriptions are about the same, where is the improvement? Where is the increased safety and efficiency for the American public?

Ms. SUYDAM. Any time a drug is approved, it is a benefit-risk ratio. That benefit-risk ratio has always to be taken into consideration.

Mr. STUPAK. But the benefit-risk ratio, according to your testimony and some previous answers, is about the same. So where is the improvement?

Ms. SUYDAM. The benefit is that the product is available to patients sooner. That's not being included in your calculations.

Mr. STUPAK. So we die sooner?

Ms. SUYDAM. No. So that people are treated and live longer.

Mr. BROWN. Will the gentleman yield?

Mr. STUPAK. Sure.

Mr. BROWN. To follow up on that point, Dr. Suydam, you still would not say that we have fallen short in any way on post-market surveillance. Sure you want to move things through the process faster, but we're simply not bulking up, if you will, or making more efficient or effective post-market surveillance.

Ms. SUYDAM. Right.

Mr. BROWN. I yield my time back.

Mr. STUPAK. The point I would add, you keep saying that these are life-saving drugs. Of the 11 that have been recalled, only one has really been sort of considered a life-saving drug. These were drugs that were approved for other things and people were dying from them. So they really wouldn't be, all 11 were not considered life-saving drugs. Correct?

Ms. SUYDAM. I think each of them had benefits, and some of them were life saving and some of them were not.

From 1981 to 2000, we had 543 new molecular entities approved. Fourteen were withdrawn. That is in that time period. So the numbers that you were citing I think are slightly different.

I would suggest that perhaps for the record we could submit a new report that we put out from our Center for Drugs on our 2000——

Mr. BILIRAKIS. Why don't you identify it, and then we can accept it.

Ms. SUYDAM. It's the Center for Drug Evaluation Research Report to the Nation 2000, Improving Public Health Through Human Drugs.

Mr. BILIRAKIS. Okay. Without objection, that will be made a part of the record.

[The report referred to is available at:]

PDF: http://www.fda.govcder/reports/rtn2000/rtn2000.pdf
HTML: http://www.fda.govcder/reports/rtn2000/rtn2000.htm
Slides: http://www.fda.govcder/reports/rtn2000/rtn2000.ppt

Mr. BILIRAKIS. Your time has expired, Bart. If you have another few seconds.

Mr. STUPAK. Sure. Let me ask this question. In late 1998, a consumer group found 27 instances in which a drug was approved over FDA staff objections, and 14 instances in which staff were told not to present data at advisory committee meetings which might adversely affect the chance of a drug being approved. Would you care to comment on that?

Ms. SUYDAM. The process of drug review and approval is one that includes many layers of review. It has the medical officer, the individual medical officer, the individual statistician. Then it moves through to the supervisor, supervisory medical officer, to the division director. Drugs are often looked at from different perspectives in terms of each of these specialties. I do not know if those statistics are correct or not, but I do know that our process is thorough and that yes, sometimes that scientists come to different conclusions about products, and that all of our scientists may not agree on any one product. It is the judgment of the Agency that has to be made in the end.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. STUPAK. Mr. Chairman, if I may, the statistics I have used have come from testimony from some people who will testify in the second panel. Also, as far as the only eight prescriptions were pulled for safety reasons in the previous 26 years, I would submit for the record Sunday Gazette Mail.

Mr. BILIRAKIS. Without objection.

Mr. STUPAK. January 7, 2001.

Mr. BILIRAKIS. Without objection, that will be the case.

[The information referred to follows:]

[Sunday, January 7, 2001—Sunday Gazette-Mail]

SPATE OF DRUG RECALLS RAISES SAFETY CONCERNS

By Knight-Ridder

In the last four years, 10 prescription drugs and a vaccine have been taken off the market after killing and injuring thousands of people.

The drugs had noble purposes, including checking diabetes, relieving pain, and fighting high blood pressure. The vaccine immunized babies against a potentially deadly infection.

For the vast majority of the 32 million Americans who took these medications, they worked—or at least caused no harm.

But for tens of thousands of patients, the withdrawn drugs were a disaster, causing temporary or permanent heart, liver, bowel or other injuries. Some injuries were so severe that the patients required organ transplants or other surgery. Thousands were fatal.

Safety withdrawals of 11 pharmaceuticals in four years appear to be unprecedented. eight prescription drugs were pulled for safety reasons in the previous 26 years.

"We are seeing the breakdown of a system that was far from perfect to begin with," said Daniel A. Hussar, professor of pharmacy at the Philadelphia College of Pharmacy. "I have a great concern that there will be even more serious problems before society says, 'Enough is enough, we need the system fixed.'"

Consumer and patient advocates, academic physicians and pharmacologists, and health-policy analysts say no step of the pharmaceutical process, from development lab to patient bloodstream, is free of blame.

They fault drug companies and the federal Food and Drug Administration for the approvals of drugs they say are questionable, and they chastise Congress for underfunding the FDA and pressuring the agency to play ball with drug companies.

But what the critics find most inexcusable is that the nation has no reliable way to track and investigate problems with drugs.

The monitoring system for drug safety is so weak and underfunded that Americans do not know for sure which drugs are causing the most or most serious problems, why they are causing problems, or what measures would help reduce the future toll, the critics say.

"When an airplane crashes and kills 200 or 300 people, it's pretty hard to hide," said Larry Sasich, a pharmacist and research analyst at Public Citizen's Health Research Group, a Ralph Nader-affiliated organization in Washington, D.C.

"But we could lose 200 or 300 people a month to deaths from adverse drug reactions in this country and not even notice it, because we have no system of adequately capturing all the serious drug reactions."

In fact, it seems likely that the monthly death toll from drugs is well above 300. Although there is no accurate count of U.S. drug fatalities, the most frequently cited estimate pegs them at 100,000 a year. That is more than twice the number of deaths from traffic accidents.

The toll is so uncertain because doctors are not required to report bad drug reactions; if they choose to do so, they inform either the FDA or the manufacturer. Manufacturers must forward any such reports to the FDA.

FDA officials, who agree that the system of post-market drug monitoring is no match for the problems, have begun to plead with Congress for more funds to beef it up.

The state of the bare-bones U.S. drug-safety monitoring system is this:

- The FDA learns of only I percent to 10 percent of serious adverse drug reactions those leading to injury, hospitalization or death—studies have estimated.
- Information about drug outcomes that could be gleaned from insurers' databases is going virtually untapped.
- A Drug problems are investigated by the FDA, and potential conflicts are created because examiners who have recommended drug approvals are also involved in withdrawal decisions.
- The FDA's annual budget for safety reviews of drugs on the market is $17 million—roughly equal to what Americans spend on prescription drugs every 90 minutes.

The questions about drug safety arise after a successful decade-long push by Congress and the pharmaceutical industry to get the FDA to approve drugs more quickly. With nearly $900 million in drug-industry funding since 1992, the FDA has increased its staff for drug and vaccine reviews by about 60 percent and has cut the time for routine drug approvals from two years to one year.

At the same time, the rise of direct-to-consumer advertising has helped spur the much more rapid use of new drugs, so that millions of people may be exposed to a drug before its risks are fully identified.

And the speedier FDA approvals mean that the European market no longer serves as an early-warning system, as it did in the late 1950s, when thalidomide use in Europe resulted in devastating birth defects; the drug was never approved here.

Given all these holes in the system, the worry is not that so many drugs—but that too few—are withdrawn, said Brian L. Strom, a physician, pharmacologist and medical-statistics expert at the University of Pennsylvania School of Medicine.

"The drugs that have been withdrawn from the market are the successes," he says. "I worry about the others that are out there, because drugs that are on the market aren't adequately monitored."

FDA and drug-industry officials dispute such grim assessments. They say the drug approval and safety monitoring systems work better than the critics acknowledge.

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said: "One reason more drugs are being taken off the market is that we are being more aggressive in pulling them off."

Bert Spilker, senior vice president at the Pharmaceutical Research and Manufacturers of America in Washington, D.C., agrees that the recent withdrawals are a

positive sign. "They demonstrate that the system works well to protect the American public," he said.

Nevertheless, in briefing material for a hearing in September, the FDA acknowledged that safety monitoring has suffered.

"Our workforce and real resources for most programs other than "drug approvals" have contracted each year since 1992," the agency wrote. "An area we have not been able to fund adequately is responding to reports of adverse events related to the use of prescription drugs."

In an interview, Woodcock said she would be happy with the $50 million budget for post-market monitoring that has been tentatively suggested by Sen. Edward F. Kennedy, D., Mass. She disagreed with calls to channel funds into mandatory reporting by physicians of severe drug reactions, and said additional money would be better spent in analyzing drug data available from insurance companies.

Post-market monitoring is a critical function because often it is not until a drug goes into widespread use that problems emerge. This fact is not a failure in either drug development or drug approval, said Alastair J.J. Wood, professor of medicine and pharmacology at Vanderbilt University.

Rather, it is a consequence of human diversity and the fact that rare events may not be ,detected in the few hundred or thousand patients in premarket trials, he says.

In the three phases of premarket testing, conditions are kept simple: the subjects are commonly people whose only medical problem is the one addressed by the drug under study, and who aren't taking any other medications.

In the real world, though, people often have more than one ailment and take more than one drug.

Because of the tremendous number of possible combinations, it would be prohibitively expensive and time-consuming to broaden the premarket tests to mimic the real world, Strom says.

So the first real-life test of a drug comes after it has been approved, and its first few years on the market are often called a Phase IV trial.

Also in Phase IV, doctors begin—quite legally—to prescribe the drugs for longer periods or in larger doses than recommended, or use them to treat conditions for which they were never tested. These experiments may reveal new ways to use a drug, but they may also precipitate new problems.

"When a drug comes on the market, that's really a controlled experiment," Wood says. "You don't know everything about the drug at that point, so you should be monitoring it carefully. And we don't have the proper system for doing that."

Moreover, the lack of information means it takes longer to discover the mechanism, such as liver damage or cardiac arrhythmia, by which a given drug causes harm—information that could help pinpoint other drugs that might cause the same problem, Wood wrote two years ago in the New England Journal of Medicine.

The prescription medications pulled from the market for safety reasons in the last four years were:

—Lotronex, which quelled the pain and diarrhea of irritable bowel syndrome. It was taken off the market in late November.

—Pondimin and Redux, either of which served as the "fen" half of the "fen-phen" diet-drug combination. Fen-phen was linked to pulmonary hypertension and heart-valve problems.

—Seldane, an antihistamine that could cause heart problems when taken together with certain antibiotic or antifungal medications.

—Posicor, for hypertension and angina, which had harmful interactions with 25 other drugs.

—Duract, a pain medication, which was implicated in liver failure, primarily in patients who took it for more than 10 days.

—Hismanal, an antihistamine, whose interactions with some other drugs, including Prozac, could cause fatal irregular heartbeats.

—Raxar, an antibiotic, which was associated with heart problems.

—Rotashield, an infant vaccine against rotavirus, which was implicated in bowel obstructions.

—Rezulin, a diabetes drug linked with at least 63 deaths among 400 reported cases of liver failure.

—Propulsid, a treatment for severe nighttime heartburn, which was associated with heart problems that killed at least 80 people and injured nearly 350 others.

Even many who are calling for more-stringent safety monitoring defend the FDA's speeded-up approval process. Strom, for example, says faster drug reviews are not less thorough but are simply compressed into fewer months.

The main concern is that safety monitoring has been squeezed by the congressionally mandated focus on faster drug approvals. Under the legislation that authorizes

industry funding for the approval process, the FDA is also required to chip in additional money each year. But Congress has not increased the agency's budget enough for it to keep up with other needs at the same time, the agency said in its September briefing paper.

And while the drug industry has been eager to fund a quicker approval process, it has steadfastly refused to provide any money for post-market safety monitoring. That refusal was understood when the 1992 law was passed and was written into the 1997 law.

The industry refuses because post-market drug surveillance is a public service and should be funded by Congress, said Jeff Trewhitt, a spokesman for the Pharmaceutical Research and Manufacturers of America.

Besides analyzing HMO databases, other suggestions for improving post-market monitoring include establishing a safety review board separate from the FDA's drug approval staff, limiting direct-to-consumer advertising of new drugs, and finding innovative ways to gather data on drug outcomes.Interestingly, many critics reject the suggestion that mandatory reporting by physicians is needed. It has been tried in various states and countries, but has not worked because doctors do not comply, said Raymond Woosley, dean for clinical research at Georgetown University Medical Center in Washington.

The FDA and some in the outgoing Congress had begun to suggest that drug safety monitoring should get a closer look in 2002, when the law authorizing industry funding of FDA activities will be up for renewal.

This time, the drug industry may be willing to talk about providing some funding.

"We would be willing to discuss this with the FDA, because we'd like to see what performance goals they would agree to in exchange for user fees, and what benefits industry would see," Spilker of the pharmaceutical industry group said. "We are open to listening to what they propose."

Mr. STUPAK. That you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Deal, to inquire?

Mr. DEAL. Thank you, Mr. Chairman.

Mr. Northrup, under the section 210, third party review process that you say has now been expanded by FDA, has it been expanded to include the 510(k)s?

Mr. NORTHRUP. It has been expanded to include all the products now that are eligible under FDAMA. That is correct. We would certainly like to see it expanded further, Mr. Deal. If I might say, the concept of third party review is not new. It is new to the FDA, but it is not new. The entire European system of regulating medical products is based on third parties, not just for review of the devices initially, but for inspection of the manufacturing facilities. We haven't seen that that system has compromised the safety of European patients.

So I think that perhaps some of the FDA's reluctance to expand the program at first was more related to the FDA's uncomfortableness with this being new to the FDA, not that this is a totally new concept that we have not seen anywhere else in the world.

Mr. DEAL. The clinical data that's associated with 510(k)s, does it allow the third party review of those? Or is it restricted under the language of FDAMA?

Mr. NORTHRUP. No. Currently FDAMA restricts review of applications to only those class 2 devices for which clinical data is not going to be required by the FDA.

Mr. DEAL. So it would require statutory change in order to expand it to the 510(k) reviews?

Mr. NORTHRUP. Yes, sir. You are correct on that.

Mr. DEAL. Would you advocate that change?

Mr. NORTHRUP. We would, and we will.

Mr. DEAL. Dr. Suydam, what is your position on that?

Ms. SUYDAM. I think that's something we would like to have more experience with the current program. We'll take that into consideration as we are considering changes in the future.

Mr. DEAL. Overall, have your third party reviews been successful and of a calibre that you find acceptable?

Ms. SUYDAM. Overall, we have found the program to be successful, and have found the calibre of reviews to be quite high.

Mr. DEAL. Does this third party review process facilitate and speed up your overall review process?

Ms. SUYDAM. Well, it certainly does take some of the workload away from the FDA, which would then leave time for people to do other things.

Mr. DEAL. I don't believe anyone gave you an opportunity to respond to one of the suggestions of Mr. Northrup, made about creating a division to deal with the hybrid type devices. Do you have any thoughts on that?

Ms. SUYDAM. I think I did mention I think having an Office of Combination Products is an idea that we will consider. I think we have a process in place right now that has been working for some time. We have been dealing with combination products for a long time. It is not necessarily a new concept to us.

Mr. DEAL. Without understanding all the intricacies of your agency, when you have a hybrid type device or product, does it require a separate review by two different groups within your agency or do they work collaboratively in that process?

Ms. SUYDAM. There is a lead center designated, and then there is a collaborative process.

Mr. DEAL. Thank you, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman.

Does the gentlelady from California wish to inquire of this panel?

Ms. ESHOO. I do. Thank you, Mr. Chairman.

First off, I want to apologize for not being here earlier from the beginning of today's hearing, which is a very important one. There is a hearing downstairs on energy. Of course as a Californian, I have a vital interest in that issue. So I ask both the chairman, the ranking member, people that are part of the panel, and the audience to accept my apology.

I have both a special interest in the issue that we are reviewing today and a special sense of pride in terms of the work that we accomplished, Mr. Chairman, on the medical device reform bill that was then folded into FDAMA.

I think in terms of the work that we have done and the effectiveness of it, not only finally partnering with the FDA, but also with people that manufacture the devices, that we really did a darn good job. Whatever we do in the reauthorization bill I think is really going to be more tweaking of the issue than having to completely reform and really do a massive reform on this. So I want to thank everyone involved, and of course, Mr. Chairman, you were a steady and important leader in this. I am proud to have been the Democratic sponsor of the bill along with Joe Barton.

The first question that I would like to ask is of Mr. Northrup. Then I would like to go to another question. I am going to state them both first, and then give you the time to answer, okay?

You testified to the importance of fair, predictable, and consistent regulatory actions during the FDA approval process. When we wrote FDAMA, we included a provision mandating that the evidence required for FDA approval to be "the least burdensome" needed to meet safety and effectiveness standards. In your opinion—and if this question has been asked before, just say it's been asked and I'll go to the record and read it—has the FDA implemented this least burdensome requirement in a timely manner?

Then I have another question and it deals with the area of reuse. Despite extensive scientific evidence demonstrating serious risks associated with reprocessing of single use devices, including several studies conducted by the Agency itself, FDA in my view has failed to meaningfully enforce key patient safety provisions of the Food, Drug and Cosmetic Act. It took substantial Congressional and public pressure to force FDA to finally publish enforcement guidelines on regulation of this potentially dangerous practice. I still remain concerned that this guidance, while a step in the right direction, and I'm always willing to give credit where credit is due. I think it's important to. I think this still continues to permit the use of many unsafe, reprocessed devices on American patients.

I would like to know about what the FDA has been actively involved in working with to develop a strategy to regulate the reprocessing of single use medical devices. Would you comment on the FDA's progress in implementing its strategy relative to the practice? Can you give me a specific example of a product where you feel that the FDA has failed to take appropriate steps to ensure the patient's safety? You may not want to answer that. You may want to answer it in writing or call me, but I think it's important for the Agency to recognize this.

What do you think can the FDA do to really address this head on? I think we are failing people in the country.

Mr. BILIRAKIS. The gentlelady has less than a minute left.

Ms. ESHOO. So I'll stop.

Mr. BILIRAKIS. Why don't we have maybe a brief response, and then follow it up, if it's all right with her, with more detailed answers in writing.

Ms. SUYDAM. There are two questions. The first is related to least burdensome. I would suggest that perhaps we were slower to act than we should have. We have had the least burdensome guidance, the most recent version just went up on our website this week, but we did have a least burdensome guidance 2 years prior to that, and have been working with industry task forces to come to some agreement about how the program should be implemented.

Ms. ESHOO. So what's on your website?

Ms. SUYDAM. The new least burdensome guidance.

Ms. ESHOO. I see.

Ms. SUYDAM. We do believe it is one that we all feel comfortable with. I think it serves the purpose and the intent of the statute.

The second thing you should know is that despite it just going up on the Web this week, it has been in effect. We have used——

Ms. ESHOO. Was that in anticipation of this hearing, do you think?

Ms. SUYDAM. No. I think the timing unfortunately or fortunately happened as it did.

I think we are already using least burdensome principles in the review of products. I have some examples that I could give you.

On the re-use, if the chairman would like, I think Dr. Feigal might be able to answer that question.

Mr. BILIRAKIS. Well, it's the gentlelady's question, but can we get it done in writing?

Ms. SUYDAM. We could do that in writing.

Mr. BILIRAKIS. In a short period of time so that it's——

Ms. ESHOO. I think it is something that obviously it's not just my interest, but I think an important interest of the full subcommittee.

Ms. SUYDAM. Yes. We understand that.

Ms. ESHOO. So I look forward to hearing from you soon on it.

Mr. BILIRAKIS. Thank you. Well, I think that with gratitude, we can excuse this panel.

Mr. BROWN. I have some questions for the record for Mr. Waxman I would like to ask.

Ms. ESHOO. Could I just yield for a moment and I could make a request on the following?

Mr. BILIRAKIS. We are going to submit. That's what I was just getting to. Questions will be submitted in writing, and we're requesting that those be responded to in a timely fashion.

Ms. ESHOO. As well as Mr. Northrup, to give him an opportunity to respond?

Mr. BILIRAKIS. Oh all of them, the entire panel, the entire panel, right.

Ms. ESHOO. Thank you, Mr. Chairman.

Mr. BILIRAKIS. I know you are always willing to do that. Additionally, as I invited you all earlier, you know there are some things can be taken care of by the departments and the agencies and what not, and some things require legislation. I was going to say litigation unfortunately, but legislation. By all means please feel free. We're in the process here of taking a good look at these things. Feel free to let us know how we can be of some help.

Thank you very much.

The next panel, if they would come forward, please. Dr. Gregory L. Kearns has already been introduced by Ms. McCarthy. He is a Professor and Chief of Division of Clinical Pharmacology and Medical Toxicology with the Children's Mercy Hospital in Kansas City, Missouri.

Can we have some order, please?

Ms. Carole Ben-Maimon, have I messed that up? Maimon? President and CEO of Proprietary Research and Development for Barr Laboratories. She is here on behalf of the Generic Pharmaceutical Association. Dr. Richard Gorman, incoming chair of the American Academy of Pediatrics, Committee on Drugs, with the American Academy of Pediatrics. Ms. Abbey Meyers, President of the National Organization for Rare Disorders. Mr. Travis Plunkett, Legislative Director of Consumer Federation of America on behalf of Patient and Consumer Coalition. Dr. Timothy R. Franson, Vice President, Clinical Research for Regulatory Affairs in the United States, Lilly Research Laboratories, and Dr. David Flockert was invited but apparently was not able to make it.

That being the case, again, your written statements are a part of the record. We would hope that you would complement them, if

you would, supplement them, complement them. The clock is at 5 minutes for each one of you.

Dr. Kearns?

STATEMENTS OF GREGORY L. KEARNS, PROFESSOR AND CHIEF, DIVISION OF CLINICAL PHARMACOLOGY AND MEDICAL TOXICOLOGY, CHILDREN'S MERCY HOSPITAL AND CLINICS; CAROLE BEN-MAIMON, PRESIDENT AND CEO, PROPRIETARY RESEARCH AND DEVELOPMENT, BARR LABORATORIES; RICHARD GORMAN, INCOMING CHAIR, AMERICAN ACADEMY OF PEDIATRICS COMMITTEE ON DRUGS, AMERICAN ACADEMY OF PEDIATRICS; ABBEY S. MEYERS, PRESIDENT, NATIONAL ORGANIZATION FOR RARE DISORDERS; TRAVIS B. PLUNKETT, LEGISLATIVE DIRECTOR, CONSUMER FEDERATION OF AMERICA; TIMOTHY R. FRANSON, VICE PRESIDENT, CLINICAL RESEARCH AND REGULATORY AFFAIRS, U.S., LILLY RESEARCH LABORATORIES, ACCOMPANIED BY STEPHEN SPIELBERG, VICE PRESIDENT, DRUG DEVELOPMENT, JANSSEN RESEARCH FOUNDATION

Mr. KEARNS. Thank you, Mr. Chairman, and members of the committee. I am pleased to be here today to testify on behalf of the pediatric provisions of FDAMA, and to come to you as a person in the trench, clinical pharmacologist who is privileged to care for children, to advocate for them, and to conduct the clinical trials that we have been talking about this morning.

Before I begin, I would like to thank specifically Representatives Greenwood and Waxman for being the champions of this, and Congresswoman Karen McCarthy, a truly great citizen of my home State.

Without question, the efficacy and safety of any drug is provided for by its study and effective labeling. This goal is not age specific. Labelling benefits adults as it does children. You have heard before that for many, many years about 75 to 80 percent of all drugs marketed in our country have not been adequately labelled for children, meaning neonates all the way up through the teenagers. FDAMA was the first thing to come along in the history of our Nation to change that.

We now have a new horizon to look to with respect to caring for our children. FDAMA was the catalyst to remove children from the status of being therapeutic orphans. This is critical because we know that our kids do not vote. They do not possess a financial or political portfolio sufficient to have them heard. This one act, FDAMA and the pediatric provisions, have made all the difference.

You have heard some about the statistics of this. I'll not talk about all of them because they are in my statement, but I want to point out that of the studies conducted to date in pediatric patients, there are 409 carefully controlled trials, all of which done with oversight of the FDA involving more than 50,000 children and having them participate in a safe manner. The information that is gleaned from this has affected every age group, all the way from children at the time of birth, as I've said before, through adolescence. The fact that 18 drugs have been labelled for children, not for trivial things but for common pediatric diseases such as allergies and fever and gastrointestinal disease, and then some criti-

cally important things such as AIDS, obsessive compulsive disorder. We're not talking about the odd things. We're talking about things for kids that are common.

As you have heard before, the activity with regard to labelling in the short 4 years of FDAMA has so outstripped anything in any other period of time, it's purely an amazing accomplishment.

Now there are folks who have been critical of these efforts and quick to identify profits. But I would like to point out some benefits, things that are hard to measure, things that are difficult to put a dollar amount to. Specific benefits that go with drugs, just a few examples, Midazolam, a commonly used sedative drug studied under FDAMA. We found through the course of those studies that there were specific adverse effects that occurred in children with certain diseases that weren't seen before.

Etodolac, an anti-rheumatic drug, used to treat the inflammation in the joints of children with arthritis. Had pediatric studies been done, we wouldn't have realized that the dose required to treat a child is twofold higher than an adult, which means children would have gotten this drug and it would have failed.

Gabapentin, a drug used to treat seizures, a very serious condition, we also found by virtue of doing studies in young children, that the dose of Gabapentin was much higher for this drug to work.

Last, Propofol, a drug used to cause anesthesia. We found serious adverse effects in the course of studying this drug in children, so much so that these have been incorporated into labelling and will in an appropriate way restrict the use in certain children. Now this is going to save tragedy. This is going to save adversity. I can't put dollar figures to it. But I can tell you with over 20 years of experience, it will make a difference.

Now proof of benefit of FDAMA in my mind has been demonstrated beyond question with respect to its impact to children. But there are some collateral benefits that we forget. The growth of infrastructures, to focus on pediatric science, the utilization of this new knowledge to improve our trials that we do, the creation of training opportunities for young people, and yes, even the generic industry is going to reap some benefits from FDAMA.

Each one of these drugs that are labelled for children at the expense of the innovator company, that pediatric labelling will carry through when that drug is a generic. Kids depend on generic drugs just the same as seniors do. That labelling will improve their utilization and their safety, and will protect the generic industry from the harm associated with poorly or unlabelled drugs.

Now it is one thing to have accolades, but the future is bright. We have to look to the future. We have to improve what we do. We have to put more money in the infrastructure. It's not just about who is getting money, but how do we spend it. There needs to be an Office of Pediatric Therapeutics within the FDA. There needs to be more emphasis through NIH, as we've heard earlier, to study drugs in children, and to create and capitalize on the advancements.

The provisions of future legislation that are aimed at this process are critical. It has been said before that children are the greatest resource, and that he who helps a child helps humanity. There is no question in my mind and the minds of my colleagues in clinical

pharmacology throughout the country, that humanity has been helped by this wonderful act. I strongly urge Congress to reapprove FDAMA and all of its pediatric provisions in tact. Thank you very much.

[The prepared statement of Gregory L. Kearns follows:]

PREPARED STATEMENT OF GREGORY L. KEARNS, PROFESSOR OF PHARMACOLOGY AND PEDIATRICS, UNIVERSITY OF MISSOURI—KANSAS CITY, AND CHIEF, DIVISION OF PEDIATRIC PHARMACOLOGY AND MEDICAL TOXICOLOGY, CHILDREN'S MERCY HOSPITALS AND CLINICS, KANSAS CITY, MISSOURI

Mr. Chairman, members of the Committee, I am Dr. Gregory L. Kearns, a Professor of Pharmacology and Pediatrics at the University of Missouri—Kansas City and the Chief of the Division of Pediatric Pharmacology and Medical Toxicology at the Children's Mercy Hospitals and Clinics in Kansas City, Missouri. As a Pediatric Clinical Pharmacologist, I have been actively involved in the design, conduct, interpretation and reporting of over 120 pediatric clinical trials involving both old (i.e., approved) and new drugs for over two decades. I am here today not representing a given professional organization or corporate concern but rather, am honored to represent the small but extremely active academic community of pediatric clinical pharmacologists: health care professionals who are privileged to not only advocate for children by direct involvement in their medical care but most importantly, as the individuals tasked to create new knowledge that is required to insure that pediatric patients are accorded the same benefits of safe and effective drug therapy as are adults. It is truly a privilege and distinct honor for me to address this Congress by voicing support for re-authorization of the FDA Modernization and Accountability Act of 1997 (known by the acronym, FDAMA) and in particular, Section 111 of this act which provides a successful, complete mechanism for the responsible and careful evaluation of therapeutic drugs critical for the treatment and prevention of disease in infants, children and adolescents.

I. INTRODUCTION

I would like to take this opportunity to express my genuine appreciation to Congress and especially, to Representatives Henry Waxman (D-CA) and Jim Greenwood (R-PA) for being the champions of one of the most significant and beneficial federal initiatives aimed at improving the health of our nation's children. I also want to sincerely thank Representative Karen McCarthy (D- MO), a truly great citizen of my home state of Missouri, for her continuing, ardent support of children wrought through words and actions.

Without question, the safety and efficacy of any form of drug therapy intended for a human of any age is enhanced through the process of careful and critical investigation that results not simply in the approval of a drug for marketing but rather, through its effective labeling. Labeling insures that prescribers and other health care professionals charged with monitoring and/or evaluating the outcome of drug therapy have complete and accurate information upon which to base decisions and execute their responsibility to patients. This general goal is not "age specific" and in the case of adult therapeutics, has been unequivocally proven to create individual (i.e., to a given patient) and societal benefit. This tangible evidence of good is, to a great degree, attributable to an evolution of therapeutic and regulatory science, much of which has been wrought by innovation within the Food and Drug Administration, the National Institutes of Health and fueled by prudent and purposeful actions of Government. Despite these important advancements for adult patients, approximately 75 percent of all prescription drugs marketed in the United States have *not* been adequately labeled for use in infants, children and/or adolescents; many of which are routinely used by physicians in attempts to improve the health of their patients. The dearth of pediatric-specific information contained in approved product labeling is not trivial when one recognizes that for the majority of these drugs, complete information to enable the most basic therapeutic requirement, the provision of age-specific/appropriate dosing guidelines, is not present. A related problem is that many medications not approved for use by children are not manufactured in dosage forms that can be readily and/or safely administered to infants and young children. For example, many medications are provided in capsule or tablet forms that cannot be swallowed by small children and/or are not available in small enough dosage increments to permit accurate, safe drug administration. These "deficiencies" can only serve in a collective manner to increase the risk of adversity in the course of providing drug therapy in pediatric patients.

It is important to note that this particular situation has not changed appreciably in the 30 years preceding enactment of FDAMA. It is for these reasons that pediatric patients were relegated to the status of *therapeutic orphans,* thereby placing the most vulnerable portion of our population at increased therapeutic risk as compared to adults. This therapeutic travesty was not perpetuated by scientific ignorance but rather, through inaction fueled by unfounded fears of harm, risk and the relative absence of a credible political and financial portfolio possessed by our Nation's children. Fortunately, FDAMA conjoined with the 1998 Pediatric Final Rule, provides a most effective "weapon" to bring pediatric therapeutic injustice to an end.

II. BENEFITS FOR CHILDREN

On November 21, 1997, former President William Jefferson Clinton signed FDAMA into law; an action that had tremendous bipartisan support given its focus on our nation's children. Included in the bill is a provision (i.e., Section 111) that encourages pharmaceutical companies to conduct specific pediatric clinical trials of drugs with demonstrated substantial therapeutic use in pediatric patients and hence, are deemed important for pediatric therapeutics. These trials are to be conducted in complete accordance with the highest ethical and scientific standards guaranteed through FDA oversight of the drug development process. This particular provision of FDAMA also allows for, but does not promise, the granting of up to six months of additional market exclusivity to new and already marketed drugs for which the Secretary of Health and Human Services (HHS) issues a written request for pediatric studies. Hence, the process associated with Section 111 is well organized, orderly and squarely focused on the responsible pursuit of information requisite for improving pediatric therapeutics. We must not lose sight that Section 111 of FDAMA was developed for children to specifically serve them and those in our society who are charged with their medical care. By doing so, it provides for the first time in the history of the United States a mechanism to insure that pediatric patients are accorded the same "therapeutic rights and privileges" that we have so carefully provided for adults.

III. FDAMA ACCOMPLISHMENTS—PROOF OF CONCEPT

The statistics associated with FDAMA are indeed both impressive and staggering. As of April 1, 2001, pharmaceutical companies have proposed to FDA the study of a total of 218 drugs which in turn, has resulted in the issuance of 188 formal written requests for the conduct of pediatric clinical trials involving a total of 154 active drug moieties. Collectively, these trials represent 409 carefully controlled clinical investigations conducted in well over 50,000 pediatric patients, with approximately 20% involving neonates and young infants and 30% involving children from adolescence down through 2 years of age. Hence, the data support involvement of the entire pediatric spectrum in a large number of clinical trials that address unmet therapeutics needs in children with markedly diverse medical conditions.

To date, FDA has granted extended marketing exclusivity to 33 drug moieties—only 21% of the total amount subject to formal written requests. Of these 33 drugs, 17 (i.e., 52%) have had major revisions of the approved product labeling; a process that may take 8-18 months after extended marking exclusivity has been granted. Of further note is that 12 of these 17 drugs (i.e. 71%) have extensive, routine therapeutic use in pediatric patients and are used to treat a wide variety of conditions that afflict infants and children including fever, allergies, AIDS, gastrointestinal reflux, obsessive-compulsive disorder, hypertension and pain. Finally, contrary to the many assertions that have appeared in the lay press over the recent past that only "blockbuster" drugs (i.e., those with greater than $1 billion in annual sales) are the subject of the pediatric exclusivity provisions of FDAMA, only 2 of the 17 drugs labeled for children meet this criteria. Without question, the degree of productivity that has occurred over 4 short years as a direct result of the provisions contained in Section 111 is remarkable and unparalleled given that in the 10 years preceding enactment of this legislation, only 11 drugs were formally (i.e., under the aegis of the FDA) studied in pediatric patients out of the 70 "promised" by the pharmaceutical industry. Thus, FDAMA works for children and works extraordinarily well.

Those individuals, groups and corporate concerns who are critical of the aforementioned success story have been quick to identify the apparent "profits" that accrue to the pharmaceutical industry as a result of the provisions of Section 111 and to estimate the "costs" to the adult segment of our society produced by delayed entry of generic pharmaceutical products to the market place. Relatively speaking, these particular "figures" are easy to generate despite their not being totally supported by fact and their dependence upon assumptions. What is more difficult to quantitate are the potential beneficial health implications (and their associated financial im-

pact) to infants, children and their families that result from the new information obtained from clinical trials conducted under Section 111 and now contained in the approved product labeling for 17 marketed drugs, all of which have a history of substantial pediatric use. Several specific examples are as follows:

- *Midazolam* (a sedative agent commonly used in medicine and dentistry): Determination of age- specific doses of a new oral liquid formulation in infants and children. Also, identification of specific adverse events associated with concomitant medicines given to pediatric patients and in infants and children with specific disease states (e.g., congenital heart disease, pulmonary hypertension).
- *Etodolac* (an anti-inflammatory drug used to treat children with debilitating rheumatoid arthritis): Demonstration of the need for a markedly increased dose in young children (i.e. approximately 2-fold higher than adults on a weight-adjusted basis) as compared to adults in order to prevent lack of efficacy from "under-dosing" in pediatric patients.
- *Fluvoxamine* (an antidepressant used to treat children and adolescents): Demonstration of a higher dose requirement only for female patients 8 to 11 years of age, thereby demonstrating both age- and sex-specific determinants of drug efficacy.
- *Gabapentin* (an oral medication used to treat a variety of seizure and other central nervous system disorders in both adults and children): Demonstration of a requirement for a marked increase in weight-adjusted dose for children less than 5 years of age as compared to older children in order to attain/maintain effective blood levels of the drug.
- *Propofol* (an intravenous agent used in adults and children to induce/produce anesthesia and for protracted sedation in adult and pediatric patients in the intensive care unit): Demonstration of potentially serious cardiac dysrhythmias in patients concomitantly treated with fentanyl (a narcotic analgesic) and also, production of central nervous system symptoms (e.g., flushing, agitation, tremulousness and hyperirritability) seen after abrupt discontinuation of the drug following prolonged infusion. These adverse events in association with possible differences in mortality in patients in the intensive care unit treated with propofol resulted in recommendation against its use (i.e., not indicated) for sedation of patients in the pediatric intensive care unit.
- *Sevoflurane* (a widely used inhaled anesthetic agent): Information added to the label warning of the potential for drug-associated seizures in children.

These illustrations provide tangible evidence of how the risk profile for many potentially useful drugs will be improved through the revelation of new pediatric-specific knowledge translated into approved product labeling—all of which was enabled by their careful, controlled study *in pediatric patients* resulting directly from the pediatric exclusivity provisions of FDAMA. Thus, the evidence is clear. Children, the intended "target" of Section 111 of FDAMA have been the direct beneficiaries of this legislation. Proof of concept has been demonstrated beyond question.

IV. COLLATERAL BENEFITS OF FDAMA

Those who question either the wisdom or importance of renewing FDAMA and maintaining the integrity of its provisions completely ignore the indirect benefits that have resulted from this legislation. Important collateral benefits have accrued to society as a direct result of the marked expansion in pediatric clinical pharmacology research wrought by the opportunities and requirements afforded by the provisions of Section 111 of FDAMA. Examples of several of these are briefly summarized as follows:

- The growth and creation of federally funded infrastructures (e.g., the National Institute of Child Health and Human Development network of Pediatric Pharmacology Research Units, the AHRQ-funded Centers for Education and Research in Therapeutics) dedicated to the conduct of not only pivotal clinical research in pediatric pharmacology (which includes phase I and II clinical trials) but also, basic and translational research in the area of developmental pharmacology and therapeutics.
- Creation of a pediatric infrastructure within the Food and Drug Administration (e.g., the "Pediatric Team") and many major pharmaceutical companies to not only implement the provisions of FDAMA but most importantly, to provide an experienced "platform" capable of working cooperatively to develop pediatric clinical investigations of sufficient rigor to answer critical questions pertaining to pediatric labeling and to augment the activities of the Review Divisions within FDA to insure that the welfare of children is served throughout the entire drug development process.

- Scientific enrichment of pediatric clinical drug trials by the inclusion of new technology and utilization of the "new biology" (e.g., molecular biology, pharmacogenetics, pharmacogenomics) in an attempt to glean the most information possible from a given pediatric investigation and to create new knowledge regarding the impact of development on drug disposition and action.
- Direct and dynamic utilization of new knowledge in developmental pharmacology (e.g., the impact of age on the activity of drug metabolizing enzymes and renal function, the impact of growth and development on drug action—both intended and adverse) to continually improve the design and scientific rigor of clinical trials conducted in infants and children without increasing the risk to subjects participating in these critically important studies.
- Development of a new "model system/approach" for the design and conduct of pediatric clinical trials that is setting the standard for this activity throughout the world (e.g., the ICH E-11 guidance, new initiatives being undertaken by Health Canada and the Canadian Paediatric Society and the European Society of Developmental Pharmacology).
- Creation of both a need and opportunity to attract young Pediatricians and other biomedical scientists to the discipline of Pediatric Clinical Pharmacology to receive the education and training necessary to fill the profound "gaps" that currently exist for properly trained individuals within academic programs, the pharmaceutical industry and government (e.g., FDA and NIH). This is critical to insure that the progress made on behalf of children during the last four years will continue and most importantly, continue to evolve during the years to come.
- Expansion of pediatric labeling to generic drug products afforded by FDAMA. It is critical for all to understand that both adult and pediatric patients benefit from the availability of high quality generic drug products. As is the case for "branded" (i.e. non-generic) drug products, a critical safeguard to insure the safety and efficacy of generic drugs in pediatric patients is the inclusion of age-specific labeling information to guide prescribers in their use. The provisions of Section 111 provide the avenue for the inclusion of pediatric information in product labeling that will be maintained when a product makes the "switch" from proprietary to generic status; the direct costs for which are 100% borne by the innovator company. Hence, the generic drug industry stands to receive considerable direct (e.g., evidence-based advertising/promotion) and indirect (e.g., reduction of risk from litigation regarding adverse drug effects in pediatric patients through inclusion of accurate pediatric data in the approved product labeling) benefits from FDAMA.

V. RECOMMENDATIONS TO INSURE CONTINUED BENEFIT FOR CHILDREN

My comments regarding the importance of FDAMA and its provisions pertaining to the health and welfare of children echo those made by several individuals on the panel with me this day and many thousands of other pediatric health care professionals who, on a daily basis, serve as advocates for children. The success of FDAMA and our collective efforts to improve the lives of children demand not only the administration of accolades but most importantly, that we all critically examine the future of this legislation so as to guarantee the successes brought about by its provisions. For FDAMA to evolve in a manner characterized by continuous quality improvement, our government will need to nurture this program to insure its effective growth and development. To accomplish this goal, I offer the following recommendations for consideration by Congress:

- Creation of a mechanism whereby drugs that are off-patent and are commonly used in pediatric patients (e.g., the list of the top 100 drugs used in pediatric practice) can be studied in children with appropriate FDA oversight so as to enable critical information pertaining to pediatric use to be included in the approved product labeling.
- The development of provisions to both shorten the time between approval of a Supplemental New Drug Application and when new pediatric information is inserted into the approved product labeling to six months. Coupled with this provision should be a mechanism to rapidly disseminate pediatric use information to both the professional and lay public.
- While FDA has implemented FDAMA to certain measures of success, it has done so without sufficient financial or personnel resources to completely accomplish these important objectives in a truly exemplary manner. As a result, challenges currently exist that range from inordinate delays in the timely review of study proposals involving pediatric clinical trials to recommendations for protocol design and conduct that may not best serve the true clinical objectives of product

labeling for pediatric patients. A solution to these challenges would be the establishment of a new Office of Pediatric Therapeutics within FDA. This new Office should be staffed with pediatricians and other biomedical scientists skilled in pediatric/developmental pharmacology and accordingly, who would be fully capable of insuring that a critical and age-appropriate approach is taken to the design of pediatric clinical trials and the interpretation of the data from them. The Office of Pediatric Therapeutics would drive the process of pediatric drug development across the FDA and through a collaborative working relationship with pharmaceutical companies, would be in a position to markedly improve the quality and quantity of all pediatric efforts within the Agency.

- Establish a provision whereby pharmaceutical companies who are conducting pediatric clinical trials pursuant to a formal written request issued by FDA would pay a "user fee" designated to specifically support the Office of Pediatric Therapeutics. The consequences of these directed user fees would provide support for the establishment of the aforementioned Office within FDA and also, would increase the number of pediatric studies requested, insure more timely review of these studies and as a result, achieve the expansion of pediatric labeling in a more expeditious fashion.
- Provision of substantial and sustaining line item support within the general NIH and FDA budget for efforts that are squarely targeted at research and education in pediatric clinical pharmacology and therapeutics. Such efforts should include marked expansion of the core funding for the NICHD Pediatric Pharmacology Research Unit Network, the provision of additional funds to NICHD to support up to 15 postdoctoral fellowship positions in pediatric clinical pharmacology on an annual basis, the creation of a standing Scientific Review Group (i.e. study section) within NIH dedicated to pediatric/developmental pharmacology and therapeutics and the allocation of additional funding within NIH (e.g., to AHRQ) to support the creation of up to seven pediatric Centers for Education and Research in Therapeutics (i.e., CERTs) within the U.S. Collectively, these actions would insure continued evolution of the scientific infrastructure necessary to insure that the science of pediatric pharmacology and therapeutics will be sufficient to service the remarkable opportunity created for our nation's children provided through the pediatric provisions of FDAMA.

Based upon all the objective evidence, it is clear that the provisions of any future legislation aimed at the drug development process must contain provisions sufficient to insure and sustain benefit for infants, children and adolescents. In four short years, Section 111 of FDAMA has done more to improve the health and welfare of children in the U.S. and abroad than any other pediatric therapeutic initiative in the history of our country. To terminate the provisions of this initiative or substantially alter them in any way would once again relegate infants and children to the status of *therapeutic orphans* and thereby, disadvantage them to the point of harm. It has been said, "he who helps a child, helps humanity" and "how a society is viewed is in large sense determined by how a society cares for its children". Thus, I emphatically urge this Congress to act prudently and decisively in support of our country's most valuable asset, our children, by renewing FDAMA and also, further increasing the level of support provided to the scientific initiatives in pediatric clinical pharmacology and therapeutics fueled by this landmark legislation.

I would like to thank the committee for affording me the opportunity to share with you my comments and recommendations. It would be my pleasure to respond to any questions that you may have.

Mr. BILIRAKIS. Thank you very much, Dr. Kearns.

Ms. Ben-Maimon?

STATEMENT OF CAROLE BEN-MAIMON

Ms. BEN-MAIMON. Good afternoon, and thank you for inviting me to testify on behalf of the Generic Pharmaceutical Association.

GPHA represents manufacturers, suppliers, distributors, and marketers of generic drugs. My prepared testimony this morning will focus on the pediatric provisions of FDAMA, provisions that I would like to comment on not only as a physician and chair of GPHA, but also as the mother of three children.

Let me begin by making it clear that GPHA supports the goal of encouraging meaningful clinical research aimed at expanding the safe and effective use of drugs in children. We all want the best

for our kids, and we all need to make sacrifices in order to ensure that their health is improved.

However, while GPHA supports the goal of encouraging clinical research to benefit the pediatric population, we believe the incentive must be balanced with competing health concerns, and must be designed to ensure that real medical advances are achieved. This type of program must ensure that children are exposed to clinical research only when the research is designed to provide meaningful results, that outcomes are proportional to the sacrifices being made by lower income, elderly patients when entry of quality, affordable, generic drugs are delayed, and that appropriate tools are used to evaluate the quality of information being obtained and the true cost and benefits.

GPHA recognizes that Congress did not pass the pediatric exclusivity law with the intention of increasing the already robust profits of major drug companies by involving children in frivolous medical experimentation. Congress' intention was clearly to provide 6 months of additional exclusivity for brand companies in exchange for serious, rigorous, original clinical studies that have the clear potential to provide needed therapeutic information. Unfortunately, we are concerned that this has not always been the outcome.

In many cases, the investment in pediatric testing and the information obtained from such testing pale in comparison to the financial windfall given to brand pharmaceutical companies and to the enormous financial burden inflicted on the consumer. We are concerned that pediatric exclusivity provisions have been in place for 4 years, and there is still no well-defined system for measuring its success, its benefits to our pediatric population, and its costs to those who need more affordable pharmaceuticals.

According to the Wall Street Journal, and I'm quoting, "The studies required to gain 6 more months of marketing exclusivity are relatively small and inexpensive, costing anywhere from $200,000 to $3 million. But the extended exclusivity that results can be very valuable. It will boost drug company sales by more than $4 billion. That $4 billion is only for the first 26 drugs tested under the program." According to the Journal, another 200 proposals to test drugs on children, worth $6 billion, are pending at FDA. Over the next 20 years, estimates are that brand name drug companies will benefit from an additional $30 billion if the exclusivity provision is reauthorized in its current form.

Congress would be well-advised to ascertain the true costs of pediatric studies conducted by brand companies so that it can make objective evaluation of the cost to society of the additional 6 months of monopoly time brand industry pharmaceuticals are awarded in exchange for these studies.

You know, Mr. Chairman, it just may be that Congress could do this for much less cost doing it through research grants to the NIH. Likewise, we need to consider the detrimental impact on the consumer when pediatric exclusivity undermines predictability in the marketplace. The generic industry has for some time been begging for predictability. Under the current law, generic companies cannot predict the time of launch for their products because pediatric exclusivity can be awarded for up to 60 days after patent expiration.

As Congress considers ways to reauthorize an incentive system for pediatric research, we ask that you be extremely careful to reauthorize a system in a way that does not perpetuate the ability of the brand industry to use it as one more tool to delay generic competition. One particular area where Congress must be particularly cautious during the reauthorization process is in the area of creating incentives for the pharmaceutical industry to conduct research on off-patent products. The goal is a worthy one. But if the system to conduct such research is going to be implemented, Congress must be sure the system does not allow the brand industry and its surrogates to delay generic competition through manipulations of labelling requirements and campaigns that question the therapeutic equivalency of generic medicines. In addition, generic companies should also be eligible for the same rewards as their brand counterparts if they should elect to perform the necessary research.

Mr. Chairman, as important as these issues are for consumers, Congress, and the pharmaceutical industry, I want to emphasize again that above all else in this debate, we support children. As a mother, I can think of nothing more important than providing incentives for meaningful clinical research that will benefit my children and the children of others. Congress should ensure that children enrolled in such studies are protected and benefit from the risks they are taking, and that corporate incentives, money and gifts given to children and their parents, do not create perverse incentives in the process.

Congress should look objectively and critically at the true value of the data being generated, and also consider the impact of sponsor grants and financial rewards to those experts endorsing and conducting such studies.

Finally, Congress should try to ensure predictability in the marketplace so that the price of pharmaceuticals can come down for consumers, and explore incentives for needed research that do not threaten market competition.

The GPHA supports your objective.

Mr. BILIRAKIS. Please summarize.

Ms. BEN-MAIMON. One more sentence. Our primary objective is to provide quality and affordable medicine to patients, including children. We truly believe there are ways to improve the system and we would like to work with you to determine that.

[The prepared statement of Carole Ben-Maimon follows:]

PREPARED STATEMENT OF CAROLE BEN-MAIMON, CHAIR, GENERIC PHARMACEUTICAL ASSOCIATION

Good morning, and thank you for inviting me to testify on behalf of the Generic Pharmaceutical Association. GPhA represents the manufacturers, suppliers, distributors, and marketers of generic drugs throughout America. My prepared testimony this morning will focus on the pediatric exclusivity provisions of the FDA Modernization Act of 1997, provisions that I would like to comment on not only as a physician and chair of GPhA, but also as the mother of three children.

Let me begin by making it clear that GPhA supports the goal of encouraging meaningful clinical research aimed at expanding the safe and effective use of drugs in children. We all want what is best for our kids and are willing to make the sacrifices necessary to improve their health.

However, while GPhA supports the goal of encouraging clinical research to benefit the pediatric population, we believe the incentive must be balanced with competing health concerns and must be designed to ensure that real medical advances are

achieved. This type of program must ensure that children are exposed to clinical research only when the research is designed to provide meaningful results, that outcomes are proportional to the sacrifices being made by lower-income elderly patients when entry of quality and affordable generic drugs is delayed, and that appropriate tools are used to evaluate the quality of information being obtained to determine the true costs and benefits.

GPhA recognizes that Congress did not pass the pediatric exclusivity law with the intention of increasing the already robust profits of major drug companies by involving children in frivolous medical experimentation. Congress' intention, rather, was to provide six months of additional exclusivity for brand companies in exchange for serious, rigorous, original clinical studies that have the clear potential to provide needed therapeutic information.

Unfortunately, we are concerned that this has not always been the outcome. We are concerned that in many cases the investment in pediatric testing—and the information obtained from such testing—pale in comparison to the financial windfall given to brand pharmaceutical companies and to the enormous financial burden inflicted on the consumer. For instance, pediatric clinical testing that does nothing more than assess children's reactions to the fifth or sixth "me-too" drug in a particular therapeutic class makes no meaningful contribution to doctors' ability to treat the relevant disease. We are concerned that pediatric exclusivity provisions have been in place for four years and there is still no well-defined system for measuring its success—its benefits to our pediatric population and its costs to those who need more affordable pharmaceuticals.

According to the Wall Street Journal, "The studies required to gain six more months of marketing exclusivity are relatively small and inexpensive, costing anywhere from $200,000 to $3 million. But the extended exclusivity that results can be very valuable. It will boost drug-company sales by more than $4 billion." And that $4 billion is only for the first 26 drugs tested under the program. According to the Journal, another 200 proposals to test drugs on children, worth $6 billion, are pending at FDA. Over the next 20 years, estimates are that brand-name drug companies will benefit from an additional $30 billion if the exclusivity provision is reauthorized in its current form.

We know that the impact on the American public is significant. The FDA has estimated that a six month exclusivity reward for pediatric research raises the costs of prescription drugs $695 million a year. These are considerations that need to be heard. Congress would be well-advised to ascertain the true costs of pediatric studies conducted by brand companies so it can make an objective evaluation of the cost to society of the additional six months of monopoly time brand industry pharmaceuticals are awarded in exchange for these studies. You know, Mr. Chairman, it just may be that Congress could achieve the results it desires in a far less costly way—doing the research on its own through organizations like NIH.

Likewise, we need to consider the detrimental impact on the consumer when pediatric exclusivity undermines predictability in the marketplace. The generic industry has—for some time—been begging for predictability. Under the current law, generic companies cannot predict the time of launch for their products because pediatric exclusivity can be awarded up to 60 days after a patent expires.

As Congress considers ways to reauthorize an incentive system for pediatric research, we ask that you be extremely careful to reauthorize the system in a way that does not perpetuate the ability of the brand industry to use it as one more tool to delay generic competition. History has taught us that if there are flaws in the law that allow for exploitation, this exploitation will occur.

One particular area where Congress must be particularly cautious during the reauthorization process is in the area of creating incentives for the pharmaceutical industry to conduct research on off-patent products. The goal is a worthy one. But if a system to conduct such research is going to be implemented, Congress must be sure the system does not allow the brand industry and its surrogates to delay generic competition through manipulations of labeling requirements and campaigns that question the therapeutic equivalency of generic medicines. In addition, generic companies should also be eligible for the same rewards as their brand counterparts, if they should elect to perform the necessary studies.

Mr. Chairman, as important as these issues are for consumers, Congress, and the generic pharmaceutical industry, I want to emphasize again that above all else in this debate, we support children. As a mother, I can think of nothing more important than providing incentives for meaningful clinical research that will benefit my children and the children of others. Congress should ensure that children enrolled in such studies are protected and benefit from the risks they are taking, and that corporate incentives, money, and gifts given to children and their parents do not create perverse incentives in the process. Congress should look objectively and critically

at the true value of the data being generated and also consider the impact of sponsor grants and financial rewards to those experts endorsing and conducting such studies. And finally, Congress should try to ensure predictability in the marketplace so that the price of pharmaceuticals can come down for consumers and explore incentives for needed research that do not threaten market competition at a time when the public is clamoring for relief from the high price of prescription drugs.

The Generic Pharmaceutical Association supports your objective. Our primary objective is to provide quality and affordable medicine to patients—patients that include the pediatric population. We truly believe there are ways to improve the current system. And we would welcome the opportunity to work with you on a matter that is so important to all of us.

Thank you.

Mr. BILIRAKIS. Thank you very much.

Dr. Gorman?

STATEMENT OF RICHARD GORMAN

Mr. GORMAN. Mr. Chairman, and members of the committee, as a practicing pediatrician for 23 years, I am beginning to see first hand in my office on a daily basis the benefits of this FDAMA and the PDUFA provisions. I am pleased to be here today to represent the 55,000 pediatricians of the American Academy of Pediatrics. The pediatric academic research community that includes the Ambulatory Pediatric Association, the American Pediatric Society, and the Society for Pediatric Research, also support and endorse the Academy's testimony.

The Academy of Pediatrics is here today to extend our sincerest thanks to Congress, and especially to Representatives Jim Greenwood and Henry Waxman, for championing one of the most extraordinarily successful Federal initiatives that have ever been accomplished for children.

As a pediatrician and health professionals, we cannot overstate how critical the passage of the pediatrics studies market exclusivity provision within the FDAMA has been toward achieving medical therapeutic advances for children. For the sake of children and infants both in the United States and internationally, we strongly believe that this legislation must be reauthorized before it expires on January 1, 2002.

To fully understand the positive impact this law has had for children, I think you are pretty well aware of what has happened for the 40 years before FDAMA was approved. Despite several aggressive efforts by the Food and Drug Administration over the past 40 years to secure more studies to support more complete usage for children, there continue to be a continuing and alarming lack of pediatric drug labelling and information.

For the decades prior to FDAMA, children were the canaries in the mine shafts that acted as the catalyst for change to improve the safety and effectiveness of medications for all the people in the United States. It would have been reasonable to assume that since children's suffering enabled these safety and efficacy changes to be made, that children would have benefited from these changes. But remarkably, that was not the case. Children suffer from the vast majority of diseases and conditions that occur in adults. Just like for adults, medications help heal conditions or ease childs' discomforts.

In a little more than 3 years, the pediatric information available through FDAMA has been dramatic. Over 188 written requests

have been made for 400 pediatric studies. Passage of the pediatric studies provision has begun a tidal wave of momentum in building the structures that will be needed to continue to get more pediatric studies and more pediatric information available and in the hands of the health care providers.

The Food and Drug Administration must be commended for the extraordinary work they have done we think in fairly and safely implementing the pediatric studies law. The benefit of these pediatric study provisions for children have been considerable. Child-friendly formulations will soon be available. It's wonderful to have a wonder drug, but if your child won't take it, it is not of much use. The pediatric formulations will be coming down through FDAMA.

Better labeling will reduce medical errors and adverse effects. Pediatric labelling can achieve considerable cost saving to the healthcare system. The FDA has calculated that if better labeling eliminated just 25 percent of the hospitalization differential to the five most common diseases that children come into the hospital for, this effect would lead to the direct medical cost savings of $228 million annually.

The success of the pediatrics studies provision must be preserved and enhanced. The AAP believes there are several proposals that will further improve therapeutics for children. We support the inclusion of off-patent drugs. The AAP strong urges Congress to include a provision for off-patent drug studies in the reauthorization legislation.

Label changes. The AAP urges Congress to explore ways to expedite the translation of the new information onto the label. We also urge the dissemination of pediatric use information. The AAP urges Congress to explore ways to disseminate information generated from the pediatric studies.

For neonates, the AAP would urge Congress to acknowledge the need to study this pediatric population if appropriate, and at the appropriate point in pediatric studies.

We support the establishment of an Office of Pediatric Therapeutics within the FDA. The AAP urges Congress to provide appropriate funding and other needed resources for a newly created Office of Pediatric Therapeutics within the FDA.

We wish to support the application of prescription drug user fees to pediatric studies. AAP urges Congress to instate prescription drug user fees for companies seeking pediatric exclusivity.

I would like to thank the committee for allowing me the opportunity to share with you the thoughts of the American Academy. Once again, I restate our strong support for the reauthorization of the pediatric studies provision within FDAMA. Thank you.

[The prepared statement of Richard Gorman follows:]

PREPARED STATEMENT OF RICHARD GORMAN, ON BEHALF OF THE AMBULATORY PEDIATRIC ASSOCIATION, AMERICAN PEDIATRIC SOCIETY, ASSOCIATION OF MEDICAL SCHOOL PEDIATRIC DEPARTMENT CHAIRS, AND THE SOCIETY FOR PEDIATRIC RESEARCH

Mr. Chairman, members of the Committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 23 years. Though I am a Clinical Associate Professor of Pediatric at the University of Maryland School of Medicine, it is through my practice Pediatric Partners in Ellicott City, Maryland where I see first-hand the pediatric therapeutic benefits of which we talk today. With over 80,000 pediatric visits annually in the five clinical

sites in four counties in Maryland, I and my partners can attest to the importance of this pediatric provision.

The pediatric academic research community that includes the Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs and the Society for Pediatric Research also supports and endorses the Academy's testimony. These societies comprise academic generalist pediatricians, pediatric researchers, and full time academic and clinical faculty responsible for the delivery of health care services to children, the education and training of pediatricians, and the leadership of medical school pediatric departments.

I. INTRODUCTION

The American Academy of Pediatrics is here today to extend our sincerest thanks to Congress, and especially to Representative Jim Greenwood (R-PA) and Henry Waxman (D-CA), for championing one of the most extraordinarily successful federal initiatives that has ever been accomplished for children. As pediatricians and health professionals we can not overstate how critical the passage of the pediatric studies market exclusivity provision within the within the Food and Drug Administration Modernization Act (FDAMA—P.L. 105-115) has been toward advancing medical therapies for infants, children and adolescents. For the sake of infants and children throughout the United States and internationally, we strongly believe that this legislation must be reauthorized before it expires on January 1, 2002.

The American Academy of Pediatrics (AAP) believes that the pediatric studies provision in FDAMA has advanced therapeutics for infants, children and adolescents in a way that has not been possible in several decades prior to passage of this law. Despite several efforts by the Food and Drug Administration (FDA) over the past 30 years to secure more studies to support more complete usage information for children, the alarming lack of pediatric drug labeling and information available to pediatricians and other health professionals continued. Statistics as recent as 1998 highlight the need for pediatric drug studies. As recently as 1998 only 20 percent of the new drugs approved by the JFDA had been studied and labeled for pediatric use.

For decades prior to FDAMA children were the catalysts for changes to improve the safety and effectiveness of medications in the United States but rarely reaped the benefits of those therapeutic advances. Children acted as the canaries in the mineshafts, dying more quickly and in greater numbers from therapeutic mishaps. The Food and Drug Cosmetic Act came into being in 1938 as a result of the death of 107 children from sulfanilamide elixir. Then in 1962 another pediatric tragedy—fetal malformation from maternal ingestion of thalidomide—led to an amendment to the FDCA that stated that drugs not only had to be safe but also effective in the population for which they were marketed.

It would be reasonable to assume that since children's suffering enabled these safety and efficacy changes to the law to occur, that children would have benefited from those changes. But remarkably, that was not the case.

Despite repeated efforts by the Food and Drug Administration to include the pediatric population in therapeutic advances, it was not until passage of the pediatric studies provision within FDAMA that we have begun to realize that goal.

Now, in just a little over 3 years, the pediatric information available through FDAMA is dramatic. We have over 188 written requests issued for companies to study drugs in children, representing over 400 pediatric studies. By comparison, in the seven years prior to FDAMA eleven studies of marketed drugs were completed, though 70 studies were promised. To complete the picture: FDA has granted 28 products exclusivity and 18 products include new labeling that provides dosage, safety and adverse event information that assist pediatricians in treating children with the correct dose and in avoiding potential toxicities when medicating children. (NOTE: The process of labeling begins after the exclusivity has been granted. The labeling process can take between 8-18 months)

II. BENEFITS FOR CHILDREN

To fully understand the positive impact that this law has had for children's therapeutics, you must first understand the pediatric situation prior to FDAMA.

Children suffer from the vast majority of diseases and conditions that occur in adults. Whether it is hypertension, diabetes, heart arrythmia, kidney infections, HIV/AIDS, pneumonia, gastrointestinal disorders, asthma or cancer—children develop these very same diseases. And so, just like for adults, medications to heal a condition or ease the child's discomfort from those disorders are needed.

But for pediatricians, there is a feeling of "Water water everywhere, but little to drink". Of all the thousands of medications found to be safe and effective for adult

disorders, only 25 percent are labeled for pediatric use. That leaves pediatricians with two difficult choices: 1) not use a medication that could provide relief and help to the child because it is not labeled for use in pediatrics or 2) use the medication off-label based on limited studies and/or the personal experiences of health professionals.

This is an untenable position which pediatricians and other health professionals are placed in: to either prescribe a drug without sufficient information or withhold treatment that may provide the best treatment for a child who is more vulnerable than adult. While off-label use of medications is a legal and acceptable part of medical practice by physicians, it should not be the standard. Unfortunately for children, off-label use is the rule, not the exception, because of the paucity of prescribing information for this population.

Passage of the pediatric studies provision has begun a tidal wave of momentum toward getting more and better therapeutic information for the pediatric population.

The Food and Drug Administration (FDA) must be commended for the extraordinary work they have done in fairly and swiftly implementing the pediatric studies law. They are working with limited staff and financial resources to carry out this unfunded mandate in which they have to accomplish an unprecedented number of pediatric research protocols, new formulations, data review, and label changes.

The benefits of this pediatric studies provision for children are considerable:

Better labeling will reduce medical errors and adverse effects. Lack of proper information for pediatric patients related to dosing, toxicity, adverse effects, drug interactions, etc. can lead to medical errors and potential injury. Medication errors produce a variety of problems, ranging from minor discomfort to substantial morbidity that may prolong hospitalization or lead to death.

Pediatric labeling can achieve considerable cost savings to the health care system. The FDA's *January 2001 Report to Congress* assessed, in very broad terms, potential cost savings to the health care industry that could follow the availability of expanded pediatric clinical information. The FDA examined the hospitalization rates for five serious illnesses (asthma, HIV/AIDS, cancer, pneumonia, and kidney infections) and found significantly higher rates for children than for middle-aged adults. FDA hypothesized that a substantial fraction of the difference between these pediatric and adult hospitalization rates for like disease conditions may be attributable to the greater range of informed drug therapies and better data on drug dosage for adults. The FDA calculated that eliminating just 25 percent of the differentials for these five illnesses would lead to direct medical cost savings of $228 million annually.

Pediatric labeling can achieve considerable savings for federal and state public and private programs. Dollars and cents arguments can not adequately provide the evidence of the effectiveness and importance of this program for children. Data are difficult, if not impossible, to find that provides evidence of the cost to a state or the federal government if a child is temporarily or permanently injured because of an adverse effect of a medication used without benefit of proper study and labeling for their age. Equally as impossible to determine is the cost society has already assumed for less than optimal care for children because medicines were not available for them. In addition, the expense of lawsuits related to such occurrences are a financial consideration.

Child-friendly formulations will be available. Even the most effective "wonder-drug" can not improve a child's health if the drug is unavailable in a formulation that a child can take (e.g., pills vs. liquid) or if the taste is unpalatable to an infant or child. Compliance with a prescription relies on the formulation. If a parent has to struggle with the child every time a dose is needed, the likelihood of completing the full prescription to obtain maximum benefit is greatly reduced.

In addition, it should be noted that new pediatric formulations can benefit the geriatric population who may also need liquid or dissolvable formulations for medications.

III. SUCCESS BEGETS CRITICISM

It is disappointing to the AAP that something that is as extraordinarily success for children has been met with unreasonable, and in some cases unfounded, criticism that is risking the reauthorization of this important program. This issue has become the "darling of the press" but the stories published do little-to-nothing to acknowledge the public health benefits that have been and will continue to be the result of the pediatric studies provision.

Criticism focuses on two main issues: 1) what is perceived as a windfall profit to the pharmaceutical industry on drugs receiving market exclusivity under the pedi-

atric studies provision and 2) the perceived increased risk of including children in pediatric trials underway through FDAMA.

"Windfall Profits" to Industry—When talking about "windfalls" from this legislation, it is essential to note that the greatest windfall has been in the area of pediatric research and information now available for pediatricians. And while it is necessary to assess the economic impact of this pediatric exclusivity program on the taxpayer, without a doubt, the greatest impact of this program will be on non-taxpayers—the infants and children of this nation.

Dollars and cents arguments can not adequately provide the evidence of the effectiveness and importance of this program for children. When considering the cost to the public for keeping higher-cost drugs on the market longer, it is reasonable to also consider the four decades when children where therapeutic orphans—with very few drugs available for their proper use. It is appropriate for the public to participate in a program that affords our nation's children with the long-overdue therapeutic information that has been granted to the adult population.

The AAP does not take lightly adding costs to the health care of individuals, but we strongly believe that a parent or grandparent would be agreeable to spending a few dollars more for 6 months in order to ensure that the drug their child or grandchild was taking had the appropriate dosing, safety and effectiveness information and that adverse events were know at the time the drug was being prescribed.

AAP acknowledges that the 6-month period of exclusivity can provide a limited number of drugs with a windfall profit from this incentive. There may be ways to explore a better balance that gets both pediatric studies done and limits the amount of profits that some of the blockbuster drugs are receiving. In seeking that possible solution, one tenet must apply—we must not lose the momentum and number of pediatric studies that are currently underway. AAP urges caution in crafting a solution that may satisfy the desire to limit industry profits but may also limit the number of pediatric studies achieved under the pediatric studies provision.

Children in clinical trials—As pediatricians our key focus is on protecting children from harm. That is why we are pushing so hard for reauthorization of the pediatric studies provision. And that is why we work to ensure that pediatric clinical trials adhere to the highest standards of scientific and ethical review. The AAP's *Guidelines for the Ethical Conduct of Pediatric Studies* is used as a foundation for conducting pediatric clinical trials.

AAP is very please with the increased number children in clinical trials and the prospect of more children participating in trials. It is a testimony to the success of this legislation. Through these important clinical trials, information is generated and then disseminated for use by pediatricians and other health professionals. What is the alternative to including children in these well-controlled, scientifically-valid pediatric studies? Having hundreds of thousands of children taking medications in office settings or at home that have not been properly studied. Subjecting children to daily uncontrolled, unregulated, and unreported studies versus including a significantly smaller number of children (thousands vs. hundreds of thousands) in controlled clinical trials is a much-preferred alternative.

In addition, there are multiple levels of scientific and ethical protections in place throughout the process of developing, conducting and reviewing pediatric studies. Through the Children's Health Act (P.L. 106-310) all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services must be in compliance with subpart D of part 45 of title 46, Code of Federal Regulations. That means that all the studies conducted as part of the pediatric studies provision of FDAMA must adhere to those same rigorous standards. In addition, each study site has an Institutional Review Board (IRB) that oversees the quality and conduct of the studies. And lastly, there is a review of the subpart D regulations underway to ensure the adequate and appropriate protection of children participating in research.

AAP believes we must be ever diligent to ensure that children are protected in clinical trials. There is certainly room to improve the protections that exist but as we move to strengthen protections, we can be confident that children in clinical trials are being cared for in optimal clinical settings.

III. NEED TO ENHANCE THE THERAPEUTIC BENEFITS

The success of the pediatric studies provision must be preserved and enhanced. The AAP believes there are several proposals that will further improve therapeutics for children.

INCLUSION OF OFF-PATENT DRUGS: In order to continue this successful therapeutic march forward for children, Congress must consider including a mecha-

nism to study OFF-patent drugs—those drugs for which the market incentives of the pediatric studies provision do not apply.

It was the intent of Congress in 1997 to address pediatric studies for on-patent drugs—those drugs for which market exclusivity was still running. As I have stated in my testimony, the AAP believes that the progress made in studies of on-paten drugs has been successful and must continue. But we still have a significant population of OFF-patent drugs that are regularly used in children but do not fall within the parameters of the pediatric studies provision of FDAMA.

The AAP strongly urges Congress to include a provision for OFF-patent drug studies in the reauthorization legislation. AAP has been in discussion with staff of several members of Congress to help develop a reasonable and appropriate way of achieving the goal of getting priority OFF-patent drugs studied in pediatric populations. We offer our expertise and assistance as Congress moves forward on this issue.

LABEL CHANGES: The timeliness and thoroughness of label changes are essential components to the success of helping children get the best medications for their disease or condition. Getting more and faster pediatric use information to the pediatricians and other physicians and health professionals that prescribe medications to children is a critical goal of the pediatric studies legislation. The AAP urges Congress to explore ways to expedite label changes.

DISSEMINATION OF PEDIATRIC USE INFORMATION: Dissemination of information is a critical component to the success of the pediatric studies provision. While label information provides a critical piece of information to pediatricians, due to space limitations on package inserts often prevent important information from being published. There are significant clinical findings that are necessary for pediatricians and physicians to review (e.g., a dose change many not be statistically significant to make it into the label but would be clinically important information for a physician to review).

AAP urges Congress to explore ways to disseminate information generated by pediatric studies.

NEONATES—The neonate population (0-1 month olds) is an extremely important and difficult pediatric group to capture in pediatric studies. While this population has not benefited significantly from the pediatric studies provision, there is no easy fix. Prior to conducting studies in 0-1 month olds, it is usually necessary to establish study information in older pediatric populations. Given the vulnerability of neonates, it is critical, both from a scientific and an ethical standpoint, to be extremely cautious in designing neonates studies. However, caution should not lead to lack of studies. Neonates also develop hypertension, lung disease, infections, and congestive heart failure. They deserve informed drug therapy for their disorders, also.

AAP would urge Congress to acknowledge the need to study this pediatric population *if appropriate and at the appropriate point in pediatric studies.*

ESTABLISH AN OFFICE OF PEDIATRIC THERAPEUTICS WITHIN FDA—In assessing the effectiveness of the pediatric studies provision, it is important to note that designing study protocols, overseeing studies, reviewing scientific data, negotiating labels, staffing pediatric advisory committees, and other related activities requires significant FDA staff resources. To date, FDA personnel assigned to these tasks have been detailed from other divisions and offices around FDA. The Food and Drug Administration has made tremendous strides, with limited resources, to implement this provision fairly and in a timely manner.

AAP is eager to increase the momentum that has been built over the last three years, and believes that in order to do that, Congress must establish an Office of Pediatric Therapeutics and provide the office with sufficient resources in order to continue and expand pediatric efforts. The Office should be charged with coordinating activities among and between review divisions and provide oversight for all pediatric activities undertaken by the FDA and coordinated with other federal agencies.

The AAP urges Congress to provide appropriate funding and other needed resources for a newly created Office of Pediatric Therapeutics within the FDA.

APPLY PRESCRIPTION DRUG USER FEES TO PEDIATRIC STUDIES—Applying prescription drug user fees to pediatric studies will assist FDA with the resources to increase the number of pediatric studies requested, conduct more timely reviews of pediatric studies and achieving labeling faster.

AAP urges Congress to instate prescription drug user fees for companies seeking pediatric exclusivity.

I would like to thank the committee for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for reauthorization of the pediatric studies provision within FDAMA.

I would be happy to take any questions you may have.

Mr. BILIRAKIS. Thank you, Dr. Gorman. I was busy here listening to staff, but honestly it had directly to do with your testimony. So I know it seemed a little rude. I apologize for that.

Ms. Meyers?

STATEMENT OF ABBEY S. MEYERS

Ms. MEYERS. Yes, sir. Thank you, Mr. Chairman.

I would like to focus on pediatric exclusivity and user fees, but I want to mention two things that weren't in our written testimony. That is, there were two important provisions of FDAMA that have been very successful. First, the notice of discontinuance, which requires companies to tell the FDA 6 months before they intend to discontinue manufacture of a drug. Originally we had asked for 1 year for this notice, but the industry negotiated it back to 6 months.

In the last year, you have probably been reading a lot about old drugs that companies are dropping and patients are actually desperate when they go to the pharmacy to pick up their next prescription, and find out nobody is making the drug any more. So this is a very important provision. FDA is putting these drugs on the Internet. Pharmacists and doctors and patients can look at that area on the Internet and find out which drugs are going to be in short supply and which have been discontinued.

In FDAMA reauthorization, we would like to see that expanded to 1 year. This will give other companies a chance to perhaps license the drug so it won't just stop being available.

Also, the clinical trials data base was in FDAMA. That is another very successful program. FDA put it on the Internet about a year ago. People from all over the world are using it to find out if there are any clinical trials on their disease. The problem there is that it only requires government-funded clinical trials. The industry doesn't put studies on unless they agree to. We really would like to see privately funded clinical trials on that data base too.

Now as for the pediatric exclusivity, it is critically important for children. Physicians need to know how to prescribe these drugs. It has been successful in enticing companies to study the drugs, but at a very high price to society.

You have to make it better. You have to fix the problems. Out of the hundreds of studies that have been done, I think somebody mentioned over 400 studies, only 18 drugs have been relabeled for pediatricians. What use are those studies if the pediatricians can't learn from them?

One of the problems is that the companies negotiate labeling with the FDA. The FDA can't tell them to change their label. Those negotiations are dragged out, 1 year, 1½ years, 2 years. Meanwhile, the pediatricians don't know how to prescribe the drug. A lot of the problem is sometimes the relabeling is bad news. It says that the drug shouldn't be used on children. The companies are generally afraid that that bad news on the label might scare doctors off. But for the sake of safety in children, Congress must mandate the relabeling. There should not be any negotiations.

The research also is being focused primarily not on the drugs that children need the most, but on the most profitable drugs. This is a real problem. Of course drugs for asthma, for example, are not

being studied. Yet millions of children are taking them, along with antibiotics and other types of drugs. Six months of exclusivity for an antihistamine or an antidepressant can mean $1 billion in sales. That is a lot of money for a drug company to make from a study that cost very, very little money. They don't have to really prove the basis of the drug. We already know it's effective. They are just looking for dosage.

Drugs with small annual sales are not being studied. Generic drugs are not being studied. So the law is costing American consumers and particularly elderly Medicare patients billions of dollars.

FDA awards exclusivity on all forms of the drug. If they study an intervenous form the drug, why should the tablets and the capsules get the exclusivity? Why should the over-the-counter drug get the exclusivity? They should only really get the exclusivity on the drug that was studied, the form of the drug.

Most important, the exclusivity should not be awarded until the label is changed. The law also has to contain human subject protections. FDA doesn't have one bioethicist on staff. It is critically important that you give enough money to the FDA to hire bioethicists. It has taken 22 years for the FDA to issue human protection rules for pediatrics. They first proposed it in 1979. It was just published, 22 years.

In a way, the drug is taxing the elderly for the sake of the young. I think that that is something that has to be looked at. We have given you some suggestions in our written testimony, to look at the possibility of tax credits to cover the cost of pediatric trials, maybe 125 or 150 percent of the cost of the pediatric trials so the companies can make some money on it, and also to award the length of exclusivity according to the annual sales of the drugs. Antihistamines should get a smaller amount than an orphan drug for a rare disease, for example.

Thank you, Mr. Chairman.

[The prepared statement of Abbey S. Meyers follows:]

PREPARED STATEMENT OF ABBEY S. MEYERS, PRESIDENT, THE NATIONAL ORGANIZATION FOR RARE DISORDERS

Mr. Chairman and members of the Committee, thank you for this opportunity to speak with you today about the reauthorization of the *FDA Modernization Act* (FDAMA). I am Abbey Meyers, President of the National Organization for Rare Disorders (NORD). NORD is a non-profit voluntary health agency dedicated to the identification, treatment and cure of rare "orphan diseases." NORD is the primary patient organization that advocated for the *Orphan Drug Act of 1983,* which is one of the most successful and important health statutes that Congress ever passed.

One of NORD's primary goals is to promote the development of new treatments and cures for rare diseases and to make these therapies accessible to patients. Under the *Orphan Drug Act,* a rare disease is defined as a health condition that affects fewer than 200,000 Americans. Keep in mind that there are more than 6,000 of these disorders, cumulatively affecting an estimated 25 million Americans. NORD's mission, therefore, is enormous and very much reliant on the successes achieved by academic scientists, pharmaceutical and biotechnology companies, medical device manufacturers, and most of all, the Food & Drug Administration (FDA), which regulates these entities.

The FDA's mission is to "protect the public health by ensuring that human drugs are safe and effective."[1] But since 1992, when "user fees" were first implemented,

[1] *Report to the Nation, Improving Public Health Through Human Drugs,* US HHS/FDA/CDER, 2000.

the public's trust in the agency has eroded. FDAMA reauthorized user fees and authorized "pediatric exclusivity," but its primary purpose was to speed the approval of more new drugs and devices, even if those drugs and devices were relatively unimportant to the public health. Just look at the seven drugs that were approved after 1993 and then removed from the market due to severe adverse reactions and deaths. Not one of these pharmaceuticals was a life-saving drug. They were drugs for heartburn, diabetes, and irritable bowel syndrome (chronic diarrhea), a painkiller, a blood pressure medicine, an antibiotic, and a diet pill. There was absolutely no reason to rush them to market. Given enough time to study the data, the FDA might have more adequately identified their risks and kept them off the market.

Consumers nationwide have begun to question FDA's true mission. Is the FDA a government agency established to protect the American public, or is it merely an extension of the pharmaceutical industry? Can we, as "stakeholders," trust the scientific judgment of the regulators when the FDA refers to the pharmaceutical industry as the agency's "customers"? I would also remind the Committee that the public is not merely a "stakeholder." We are the ones who may live or die based on the FDA's decisions.

The *Prescription Drug User Fee Act,* or PDUFA, was enacted to provide sufficient funding for the agency to hire the additional staff needed to review new drug applications at a quicker pace. In exchange for user fees, the FDA was given the responsibility (of meeting very specific "performance goals." These performance goals, often referred to as "deadlines," have resulted in what some FDA officials refer to as a "sweat shop atmosphere." For example, for each new drug application submitted to the FDA, reviewers must master volumes of data in less than six months or a year, while juggling many other tasks.[2] They quickly burn out from the intense pressure to perform, and often leave the agency in less than two years and go to industry to earn higher salaries.[3] Performance goals create another unintended consequence—companies have an incentive to delay submission of voluminous data, putting the agency under tremendous pressure to meet user fee deadlines without adequately analyzing the data. It appears the industry has the best of both worlds—they get their quick approvals AND they hire the scientists trained by the FDA.

Given the fact that pharmaceutical firms considers PDUFA "their" program (and I quote, "The time to approval in the review process has been coming down markedly since WE instituted the program in 1992"), it is probably a political reality that PDUFA will, in fact, be reauthorized because it is seen as a way to get products to market quicker with minimal erosion of patents.[4]

But before PDUFA is reauthorized, we feel that consumers and patients must have assurances that the primary mission of the FDA is to protect and serve the American public—not to improve the financial picture of the pharmaceutical industry. As you consider reauthorization of FDAMA, therefore, we ask that you consider the following suggestions:

THE POLITICS OF FDAMA

FDAMA was enacted during the Clinton administration, and some suspect it fell victim to the "reinventing government" initiative. Congress wanted to cut back federal spending, so "user fees" were implemented under PDUFA in 1993. FDAMA incorporated and reauthorized user fees in 1997 and, at the same time, was supposed to make the

FDA more "user friendly" to the drug and device industries. Government regulatory agencies were told to be more cooperative with the industries that they regulate, and President Clinton specifically asked FDA administrators to trust industry as "partners, not adversaries."

Many consumer groups opposed FDAMA because they felt it would lower the safety and efficacy standards for new drugs, inflate FDA's resources for new drug reviews, and in turn deflate resources in other areas of the agency that are critical to the public's health. FDA would no longer be the "gold standard" for the world's health authorities, and nothing in FDAMA indicated that American consumers would be the agency's real "customers." Thus, the agency would not become more "user friendly" to the public. In fact, Congress, FDA and the regulated industries negotiated the law, and consumers were specifically omitted from the debate.

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[2] *How a New Policy Led to Seven Deadly Drugs,* Los Angeles Times, April 17, 2001, by David Willman.

[3] *FDA/Industry Face-Off in Preliminary PDUFA III Discussions,* FDA Week, April 20, 2001, p. 13.

[4] *User Fees for Faster Drug Reviews—Are They Helping or Hurting the Public Health,* FDA Consumer, September-October 2000, p. 26.

The changes that FDAMA brought about were NOT intended to enhance or protect the public's health. In fact, the agency had implemented critically important rules in the 1980s under Commissioner Frank Young during the Reagan administration for giving "priority reviews" to breakthrough drugs for serious and life-threatening diseases. But the pharmaceutical industry lobbied Congress for FDAMA on the basis that the FDA was taking too long to get "life-saving" medicines to the public. The truth was that life-saving medicines were already being speeded through the process, but the standard "me-too" drugs were taking more time than the industry wanted. Undoubtedly, FDAMA would not have been enacted if the arguments had been framed in terms of "speeding new diet pills to the market."

In 1988, only four percent of new drugs were approved first in the United States. By 1998, 66 percent of all new drugs were approved first in the USA.[5] But, being first out of the gate does not necessarily mean you will win the race. When faulty drugs are rushed to approval, the "prize" for being first may be unnecessary exposure to negative side effects or death.

REVIEW TIME VS. SAFETY

The approval time for New Drug Applications (NDA) has decreased dramatically since PDUFA was first enacted. Back in 1993, the medial approval time was 24.1 months. In 2000, that figure plummeted to 11.2 months, or about 54 percent.[6] If you look just at those statistics, I suppose you could say that PDUFA has been a resounding success.

However, there have been far too many withdrawals of marketed drugs after they have killed and disabled people, casting a serious shadow over the agency's credibility and competency. The publicity fueled by these withdrawals has further cast doubt on whether the user fee program is in the public's best interest. Based on those withdrawals, it is quite apparent to many that the FDA should not be subjected to the pressure cooker atmosphere created by PDUFA. Products are being rushed through the review process and, as a result, consumers are being exposed unnecessarily to sometimes dangerous and life-threatening drugs. Human beings are not guinea pigs, gentlemen. When FDA determines that a drug is both safe and effective, we take them at their word.

NORD believes the agency's success must NOT be measured by the speed of its work, but rather the completeness and scientific soundness of its work. In fact, some of the drugs that have been removed from the market in recent years might have been approved with more adequate labeling if FDA had enough time initially to recognize adverse effects, and to require appropriate labeling when the drugs were first approved. FDA reviewers must be given the latitude to review new drug applications at a decelerated rate if it is deemed scientifically and/or ethically necessary, especially when a drug is not a life-saving therapy. Let the reviewers do what they have trained years to do. Of course, everyone wants to see life-saving drugs come to market quickly, but only if they have been determined to be safe and effective. Remember the first law of medicine—*First do no harm.*

The agency should not be forced to take a "one size fits all" approach to drug approval; it is wrong to require FDA to spend the same amount of time to review all standard or priority drugs and biologics. Some will need more time. Some will need less. Safety and efficacy should be the only true measure of whether a drug is approved or not.

DRUG LABELING

It is my understanding that eleven or more drugs have been removed from the market since 1993, but seven of them were first approved for marketing after 1993. In many of these cases, FDA "negotiated" labeling changes with the manufacturer, and left the drug on the market, hoping that doctors would notice the new warnings and prescribe the drug properly. Of course, health care providers usually don't reread labeling once a drug has been on the market, so after more deaths and serious adverse events, the FDA finally banned the drugs.

The fact is the FDA seldom orders a company to change its label. Rather, they "negotiate" with companies over wording, and these negotiations can last for many months while manufacturers try to get wording that will have the most positive spin to enhance their marketing plan. We believe that FDA should be given the authority to order immediate labeling changes without negotiations. FDA's role is to protect

[5] *Quickened pace of drug approvals by FDA taking toll,* by David Willman, Los Angeles Times, December 28, 2000.

[6] *Approval Times (in months) for NDAs and NMEs Approved,* Calendar Years 1986-2000, FDA, CDER/ORM.

the public's health. Manufacturers should not be telling the regulators how to regulate the regulators!

ADVERSE EVENT REPORTING

The United States has a voluntary system of adverse event reporting (AER). It relies on doctors, hospitals, consumers and manufacturers to report adverse events, but the FDA doesn't have sufficient resources to analyze the data and try to identify red flags that may point to public health disasters (e.g., heart problems caused by diet pills). Even with the incompetencies of the current AER system, voluntary reports of adverse events from pharmaceuticals rose 89 percent between 1993 and 2000.[7] This alone should signal that too many new drugs are reaching the market before they are adequately studied. The rush to market is NOT for the sake of the public; it is solely for the sake of the industry.

Reauthorization of PDUFA must change this mindset and focus the law on public health **protection** and **enhancement,** including stronger FDA authority to analyze adverse events and to protect human subjects in research. To date, the FDA has no bioethicists on staff, no authority to stop a clinical trial if an informed consent document is inaccurate or misleading, or even if the study is unethical. Most clinical research today is funded by the industry, not by the government, and privately funded research does not have to obey the Common Rule. FDA should have the authority to enforce patient protections for privately funded research, and it must be given the funds to do this. Moreover, Congress should mandate adverse event reporting so that severe reactions to drugs can be tracked.

POST-MARKETING SURVEILLANCE

Under FDAMA the FDA can **ask** manufacturers to perform post-marketing studies, but such studies are not mandatory. Even if the manufacturer agrees to such studies, the FDA does not have the authority to penalize the company if the studies are not conducted, and the FDA is the first to admit they don't even know if companies are doing them. FDA usually asks for post-marketing studies when they have rushed a priority drug through the approval process, but there are still unanswered questions. Often, once these drugs are used in the real world where people take other medicines, or have other illnesses, adverse events will occur.

At a recent Food and Drug Law Institute educational conference, industry argued that the FDA "has no jurisdiction in the area of risk management". We happen to agree with the FDA that the industry's position is "disingenuous." At the same conference, Jane Axelrad, Associate Policy Director for the FDA, said, "Drug companies have task forces out there bombarding doctors with details about drugs and this—along with direct-to-consumer advertising—is clearly influencing prescriber practice."[8]

We ask that you make these post-marketing studies **mandatory,** and give the FDA the authority to assess penalties when companies do not do what they have promised to do. Post-marketing surveillance does not "step on the toes of the practice of medicine." Rather, it goes to the very heart of the mission of the FDA—to protect American consumers.

USER FEES

As prescribed by law, user fees can be employed for very specific purposes ONLY. They cannot be used for critically important public health functions such as adverse event monitoring or advertising and marketing enforcement. Nor are they assessed for generic drugs, medical devices, food importation or cosmetics. So, for almost a decade, the FDA has been forced to beg, borrow and steal staff and resources, robbing Peter to pay Paul, to the detriment of other vital agency operations. With the dangers of Mad Cow disease, bioterrorism, and bioengineered foods looming in our future, the agency cannot possibly meet its mandate with insufficient resources! Our nation is poised for a public health disaster because the FDA simply cannot do its job. **Congress must adequately fund the FDA or institute user fees for all other areas of FDA's public health responsibilities.**

User fees have enabled the FDA to cut new drug approval times in half, but they have also created a financial dependence by the agency on the industry it regulates. Understandably, the pharmaceutical industry wants to continue the user fee program. Every day that the industry can save on the new drug approval process is one more day they can sell their drug before their patents expire. However, the

[7] Los Angeles Times, April 27, 2001.
[8] ibid.

FDA's dependence on the user fees that companies pay creates a perceived conflict of interest that may compromise the health of the American public.

The integrity of the US drug approval process is at risk, and the implications of the loss of public trust here and around the world are immense. The FDA should not have a direct fiscal interest in optimizing user fees, because this practice has led to public distrust. Speaking for myself, I would think twice before being one of the first patients to take a newly marketed drug. I cannot trust that FDA reviewers in a "sweat shop atmosphere" adequately reviewed the product.

The only drugs given priority review at the agency should be treatments for *life-threatening* and *untreatable diseases,* drugs for patients who are *not helped by existing treatments,* or drugs for serious diseases that are *safer* or more *effective* than current therapies. In fact, we would recommend that you examine the FDA's definition of "clinical superiority" in the *Orphan Drug Act* regulations. Priority reviews should be given only to drugs that are substantially "different" from the drugs currently on the market and ones that have been clearly shown to be safer, or more effective, or to offer a significant contribution to patient care (e.g., an oral version of an injectable drug).

FDA's annual measure of success or failure should NOT be the number of drugs it approves during a given year, but rather the medical and public health **advancements** that each drug represents. The speedy approval of drugs for diagnoses that don't exist in medical texts, more cosmetic, "me-too," or lifestyle drugs, does not represent a major improvement in public health.

Some drugs should take more time, and some should take less, depending on the quality of scientific data. Since the Reagan administration in the 1980s, the agency has had adequate tools to make investigational drugs available to patients who need them (e.g., compassionate use, treatment IND's, early access programs, etc.).

In summary, FDA needs **more flexibility on spending user fees** (they should not be confined to new drug reviews), and the onus is on Congress to either institute user fees for other industries, **or appropriate sufficient funds** for all of the other critically important public health responsibilities of the agency.

PEDIATRIC EXCLUSIVITY

For rare diseases, the pediatric use of drugs that were developed for adult health conditions is an absolute necessity. Most children are healthy and may require the normal cough and cold remedies, antibiotics, and perhaps asthma drugs. Serious health conditions in children are rare, and medicines to treat their ailments are very rarely labeled with information about pediatric dosage.

NORD agrees that the pediatric exclusivity provision "has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling."[9] We also agree with the proponents of the provision that it should be reauthorized by Congress in order to ensure that all children have access to medications needed to protect and preserve their health. But we feel that other types of incentives should be examined in the congressional debate, and careful fine-tuning of the law is needed.

We are delighted that the FDA has "drawn a line in the sand" against the industry's practice of enrolling healthy children in clinical trials, and it will no longer grant pediatric exclusivity if there is no potential benefit for children who participate in such studies.[10] We say bravo to the FDA! The prohibition against including healthy children in clinical trials has been in effect since the 1970s (*The Belmont Report*), and it is part of the *Common Rule* and the *Declaration of Helsinki.* However, privately funded medical research does not have to obey the *Common Rule,* so for the past decade American children have been exposed to risks that are unacceptable in other industrialized nations of the world.

We believe there have been other unintended negative aspects of the pediatric exclusivity provision that should be addressed by this Congress.

- The *Wall St. Journal* reported that six months of pediatric exclusivity for the antihistamine Claritin amounts to $975 million dollars in sales to the manufacturer, six months of the antidepressant Prozac sales amounts to $831 million, while highly used generic drugs like the asthma compound Albuterol, and antibiotics like ampicillin, are not being studied in children at all.
- It is estimated that over 20 years of pediatric exclusivity will cost Americans $13.9 billion, while brand name drug makers will earn $29.6 billion, and

[9] *The Pediatric Exclusivity Provision, January 2001, Status Report to Congress,* Department of Health and Human Services, U.S. Food and Drug Administration.

[10] *FDA Week,* April 25, 2001, p.3.

generics will lose $10.7 billion. Distributors and pharmacies will lose $4.9 billion.

- When FDA awards pediatric exclusivity, the exclusivity is awarded for the active moiety rather than just the pediatric indication. In one case a company studied an intravenous form of an indigestion drug on children, but the exclusivity applied to all liquid and pill forms, and even the over-the-counter version. Thus, the pediatric exclusivity provision is like a tax that Medicare-dependant grandparents have to pay for the sake of their grandchildren, by paying inflated prices for a longer period of time.
- Of the studies that have been done, and the exclusivity awarded, **only a tiny proportion of those drugs have been re-labeled for pediatric usage.** What use is a study when information about dosage adjustments and side effects is not available to pediatricians? **We believe that exclusivity should NOT be awarded unless and until the label is actually changed.**
- The law is inequitable because it leaves out huge categories of drugs (including biologics) that children need, that will never be studied. This includes generics and even patented drugs with small annual sales. The problem is that **pediatric exclusivity encourages companies to study their most profitable drugs, but not the drugs that have the most intense medical need for children.**
- Although we applaud the FDA's recent issuance of an interim rule providing additional safeguards for children in clinical trials, the pediatric exclusivity provision, as currently written, contains no human subject protections. Questions continue to be raised about clinical research in the pediatric population, as reports of large cash payments to parents and other questionably ethical inducements are reported in the press.
- The pediatric exclusivity provision actually bribes companies to do what they ought to be doing as decent corporate citizens. Until 1997, companies refused to conduct the studies until they saw a way to increase profits **well in excess of what these studies cost.** The FDA now says it will require all new drugs to be tested in children and can demand that trials be conducted when the agency feels a treatment will be applicable to children's diseases. However, **drug companies are suing the FDA to stop this!** The industry says the FDA has no authority to require companies to study their new drugs on children. We ask Congress to **give the FDA this authority** so the agency can protect the health and welfare of our children. It is regrettable that the government must force the industry to be good corporate citizens—a very sad state of affairs indeed.
- We also suggest that in the congressional debate about reauthorization of the pediatric exclusivity rule, you look at other options that will not tax the elderly with high drug prices, for the sake of the young. For example, instead of preventing lower cost generic drugs from reaching the market when brand name patents expire, why not award a large tax credit to companies that perform the clinical trials necessary for pediatric labeling? Perhaps a tax credit of 125 percent of the costs of the studies would entice companies into supporting the trials, and even reward generic companies who do pediatric investigations on older drugs. **In fact, Congress' highest priority should be the development of incentives, or appropriation of funds, to encourage pediatric research on the generic drugs most needed by children.**

SUMMARY

In summary, Mr. Chairman, the FDA is losing the public's trust because it does not have the resources to do its job. The strict deadlines for new drug reviews are forcing drugs out on the market before FDA scientists adequately review them. Companies that do not feel their drugs are reviewed properly resort to lobbying Congress. There ought to be a firewall between industry and the FDA so that scientists can make their decisions based solely on scientific grounds. Yes, the FDA should be accountable, but so should the pharmaceutical industry. Drastically limiting review times while expecting more drugs to get approved is not the right way to measure success: It is a prescription for disaster.

We ask Congress to take a very careful look at the law and recognize that FDA's primary role is to **protect and enhance the public's health.** A more careful new drug review process will do much to avoid public health disasters in the future. FDA has had adequate mechanisms to allow very promising new drugs to reach the public before they are approved for marketing, but this should only be for life-threatening and serious diseases with no other treatment alternatives. We should not be rushing baldness remedies and indigestion drugs to market.

We also ask Congress to appropriate sufficient funds for other FDA initiatives. It has been reported that funding for non-PDUFA programs is down 20 percent, while PDUFA-related programs have seen increases of 27 percent. The exaggerated emphasis on new drug approvals saps resources from the agency's other public health functions.

Mr. Chairman, people with rare diseases desperately need new drugs to save their lives and prevent disability, but not at the expense of safety and efficacy. When we spend our hard earned money on a treatment, we want to know first if it is safe, and second if it is effective. **Nothing else matters.** Those with very serious and deadly illnesses are often willing to take higher risks (e.g., cancer chemotherapy drugs), but only if our doctors know what the side effects are and how to manage them. Our lives depend on the FDA, and if the agency cannot do its job, it puts our lives in jeopardy. We trust that Congress will use its wisdom to bring credibility back to FDA and bolster its public health mandate.

I thank the committee for its invitation to express the interests of people with rare diseases in the debate about reauthorization of FDAMA, including PDUFA and pediatric exclusivity.

Mr. BILIRAKIS. Thank you, Ms. Meyers. You gave us an awful lot of suggestions. I jotted down some of them. The rest of them are all in the record. In fact, I have been talking to the staff about one of them right now.

Mr. Plunkett?

STATEMENT OF TRAVIS B. PLUNKETT

Mr. PLUNKETT. Good afternoon. Mr. Chairman, Mr. Brown, my name is Travis Plunkett. I am the Legislative Director of the Consumer Federation of America. I am here today on behalf of the Patient and Consumer Coalition, an ad hoc coalition representing a diverse array of consumer and patient organizations. I would like to thank you both for conducting this much-needed hearing on the Food and Drug Administration Modernization Act and its impact on Americans nationwide.

I will focus my comments on PDUFA, the Prescription Drug User Fee Act. Has PDUFA II, as reauthorized in 1997, been a success? Well, if success is only measured by the speed of drug approval and the number of drugs getting onto the market, the answer is a resounding yes. But the FDA's responsibility under the law is to ensure that new drugs and devices are safe and effective. By this measure, PDUFA II has some serious problems.

Now clearly there are very important public health benefits to be gained from faster approval of certain new drugs. This includes drugs that treat serious and life-threatening conditions, drugs that provide relief for patients with illnesses or disabilities, that are resistant to existing therapies, or drugs that are less toxic than currently available therapies.

Most Americans, however, would agree that a lifestyle drug like Viagra or a me-too drug that is just a mere copy of a bestseller does not need to be rushed to market as quickly as say an important new anti-cancer agent or an enzyme replacement therapy for genetic disease. The fact is that as the FDA's dependency on fees paid by the regulated industry has grown, so have the number of recalls and warnings.

Mr. Chairman, I don't raise this issue lightly. We can talk about in questions why it is much more important to look at the number of recalls and warnings, the number of Americans who have been affected, as opposed to the rate of withdrawal. That is, the percentage of drugs withdrawn compared to the number of new drugs on

the market. It is a much more effective way of evaluating whether PDUFA has increased safety and health.

Eleven prescription drugs have been pulled from the U.S. market in the last 3½ years for safety reasons. This is by far the most such actions taken in any comparable period. Only one of these drugs, an antibiotic, had lifesaving potential. But it was later deemed to be unnecessary because other safer antibiotics were available. More than 22 million Americans took these drugs. Just last week an anaesthetic was removed from the market after five people were reported to have died.

Now if we look at these withdrawals a little more closely, we find that of those 11 drugs, eight were approved after PDUFA took effect, first took effect in 1993. According to the Pulitzer prize wining investigation by David Willman at the Los Angeles Times, seven of these drugs are suspected in just over 1,000 deaths. In overall, these adverse events, as they are called, have increased in reporting—these are voluntary reports, as you heard, to the FDA—by 89 percent from 1993 to 2000.

One of the major reasons why these drugs were improperly allowed onto the market is because PDUFA has very stringent decisionmaking deadlines that we view as inappropriate, potentially dangerous, and open to manipulation by the drug industry. Now the FDA takes pains to explain that these are performance goals, that they are focused on decisionmaking and not approving drugs. But there is evidence to suggest that in the real world, FDA employees have been under tremendous pressure to meet not just decision deadlines, but also to approve drugs.

I will just cite the LA Times story to you again. You may want to look at this. It includes quote after quote from retired and former FDA employees, that they were under tremendous pressure from FDA officials and because of the deadlines under the law to approve drugs, not just make decisions about them.

These deadlines forced the agency to take a cookie cutter approach to drug approvals. It is just not in the public interest to require the FDA to act at the same speed for all standard or priority drugs and biologics. Some should get more time. Some should receive less.

Moreover, it's just inappropriate to give a regulated industry this kind of dominant voice in determining what will be the process for oversight of that industry, as was done in crafting PDUFA in 1997. I would like to commend both of you for doing it differently this time, for having a spectrum, a diverse array of folks offering a variety of opinions on PDUFA.

The end result is that the regulated industry controls not only the funding and the timing for new drug approval, but the measurement tools that are used to determine the FDA's success or failure in this matter.

I will close with my remarks there, and answer any questions you have later. Thank you once again for having this hearing.

[The prepared statement of Travis B. Plunkett follows:]

PREPARED STATEMENT OF TRAVIS B. PLUNKETT, LEGISLATIVE DIRECTOR, CONSUMER FEDERATION OF AMERICA, ON BEHALF OF THE PATIENT AND CONSUMER COALITION

Good morning. I am Travis Plunkett and I serve as the Legislative Director of the Consumer Federation of America. I am here today on behalf the Patient and Con-

sumer Coalition, an ad hoc coalition of patient and consumer advocacy organizations working to insure greater access to safe, effective affordable drugs and medical devices. The coalition also focuses on enhancing the ability of the Food and Drug Administration to protect public health through effective enforcement of the law. (Please see the attached for the coalition's mission statement and founding members.) This testimony is endorsed by the following members of the coalition: Center for Medical Consumers, Consumer Federation of America, Gay Men's Health Crisis, National Consumers League, National Organization for Rare Disorders, National Women's Health Network, Public Citizen, UAW and the U.S. Public Interest Research Group.

I would like to thank Chairman Bilirakis and Ranking Member Brown for the opportunity to offer comments on the impact of the Food and Drug Administration Modernization Act (FDAMA) on consumers and patients nationwide. We urge the subcommittee and the full committee to have several hearings to evaluate both the impact of FDAMA on public health and safety, as well as the range of possible changes that could improve it. I will focus my comments on a key component of the Act: the expansion of the Prescription Drug User Fee Act (PDUFA.) I will also comment briefly on the "pediatric exclusivity" provision that grants additional patent life to drug manufacturers that conduct clinical tests on the effect of their drugs on children.

THE PRESCRIPTION DRUG USER FEE ACT

As you know, PDUFA was first enacted in 1992 to address concerns about the length of time it took for new drugs to treat life threatening and disabling conditions to be reviewed and approved by the FDA. While the issue of new drug approval time had been a contentious one for several decades, the experience with HIV/AIDS convinced many that there was room for improvement. PDUFA recognized the reality that the resources of the agency were constrained and that a shorter approval process would require considerably more staff devoted to the drug review process. User fees were imposed upon industry that would fund the additional agency resources needed to speed up the review and approval process.

PDUFA was reauthorized in 1997 as part of the FDAMA. However, this iteration introduced increasingly stringent "performance goals" requiring that the FDA meet tight review deadlines. It even includes stipulated time frames for scheduling of meetings and response to industry requests. For example, the 1997 PDUFA establishes a performance target that requires FDA to review 90 percent of priority new drug applications within 180 days and non-priority new drug applications with 10 months. These mandates were insisted upon by the industry that argued that these "measurables" were necessary to ensure that the user fees they paid were not dispersed to fund other agency activities.

As a result of the 1992 and 1997 legislation, the FDA has dramatically increased the amount of resources it devotes to new drug and biologics review and approval from $120 million in 1992 to a projected $325 million in FY 2002. In FY 2002, it is estimated that a record half of the resources required for new drug approvals will come from user fees paid by the regulated industry.[1]

Has PDUFA been a success? Well, if success is only measured by the goals mandated in 1997, the answer is a resounding "yes." The time for approval has decreased from a median of slightly less than two years in 1992 to less than one year at present. A higher percentage of applications are now approved; 80 percent compared with only 60 percent in 1992.[2]

But the success of a drug review and approval process should not be measured by speed and approval rates alone. The FDA's responsibility under law is to ensure that new drugs and devices are safe and effective. That is the true public health responsibility of the agency by which its success or failure must ultimately be measured. We believe that the effect of PDUFA II on public health and safety is a matter for grave concern.

1. PDUFA creates a financial dependence by the FDA on an industry it regulates. This is a conflict-of-interest that could compromise drug safety. Our organizations recognize that PDUFA has provided the agency with the resources to speed up new drug approvals since 1993. Clearly there are public health benefits to be gained from faster approval of *certain* new drugs. These include medications that treat serious and life-threatening conditions, drugs that provide relief for patients with illness or disability refractory to existing therapies, or drugs that are less toxic than currently available therapies.

[1] Food and Drug Administration, "PDUFA Background Information," August 2000.
[2] Ibid.

However, the FDA's direct fiscal interest in optimizing user fee income to achieve speedier approval times and get more drugs through the approval process in each budget year creates an obvious tension with its responsibility to assure the highest degree of safety and efficacy of new products. As mentioned above, the FDA's dependency on fees paid by the regulated industry has grown dramatically since fees were first initiated in 1993. The integrity of the drug approval process is what is potentially at risk and, as a result, the safety of the millions of Americans who use prescription drugs could be compromised.

The growing number of recalls and warnings related to newly approved drugs has reinforced our concerns. The agency has attempted to demonstrate that there is no relationship between faster approval times and more frequent recalls or additional safety warnings. However, there have been too many recent withdrawals of marketed drugs that have killed and injured people that have cast a serious shadow over the integrity of the approval process. Eleven prescription drugs have been pulled from the U.S. market in the last three and one-half years for safety reasons, by far the most such actions taken in any comparable period. More than 22 million Americans took those drugs. Just last week, the anesthetic Raplon was removed from the market, after five people were reported to have died from bronchospasm.

These eleven drugs include three that were approved before PDUFA took effect in 1993, but the withdrawn drugs Lotronex, Propulsid, Rezulin, Raxar, Posicor, Duract and Redux have all been approved since 1993. According to the Pulitzer Prize-winning investigation by David Willman of the *Los Angeles Times,* these seven drugs are suspected in 1,002 deaths.[3] This is based on the FDA's reporting of "adverse events," which doesn't prove that a particular drug caused a death; it is merely a "primary suspect." However, adverse events reports are also voluntary, so the true number of fatalities caused by these drugs could be much higher. Adverse events reported to the FDA increased by 89 percent from 1993 to 2000.[4]

Moreover, we are particularly concerned that, to date, the risks posed by these drugs have fallen disproportionately on women. In January, the U.S. General Accounting Office (GAO) reported to Congress on the subject of drug safety with the significant finding that most drugs withdrawn in recent years had greater health risks for women. Specifically, the GAO investigation found that, "Eight of the ten prescription drugs [withdrawn from the U.S. market since January 1, 1997] posed greater health risks for women than for men" and that four of the drugs withdrawn "had more adverse events in women even though they were widely prescribed to both women and men."

Only one of the drugs withdrawn from the market since 1993, the antibiotic Raxar, had lifesaving potential. It was ultimately determined to be unnecessary because other, safer antibiotics were available. Willman's investigation also included reports from a number of former FDA employees that the need to act quickly—as required by PDUFA—and the demands of FDA officials, put them under enormous pressure to approve new drug applications, whether they felt the drugs were safe or not.

As if to confirm our fears, the term "customer" has crept into the FDA's characterization of the prescription drug industry. We are very concerned that an agency chartered to safeguard the public's health would characterize the industry it regulates as its primary customer, and itself as a "supplier" of services (namely new drug review and approval.) It is the public, not the drug industry, that should be the FDA's "customer." The medical and public health consequences of faster drug approval are the appropriate measure of PDUFA's successes and failures, not the tabulation of the average number of months a drug requires for approval.

2. PDUFA's performance goals are inappropriate, potentially dangerous and open to manipulation by the drug industry. Although the FDA takes pains to explain that the performance goals mandated under PDUFA are for decision-making, not approval, these goals put the FDA under tremendous financial pressure to move very quickly on the overall approval process. Here's what William B. Schultz, a former deputy commissioner at the FDA told the Los Angeles Times about PDUFA deadlines: "You can meet the goal by either approving the drug or denying the approval. But there are some who argue that what Congress really wanted was not just decisions, but approvals. That is what gets dangerous." Dr. Solomon Sobel, the former director of the FDA's metabolic and endocrine drugs division told the *Los Angeles Times* that deadline pressure under PDUFA was not just to

[3] David Willman, "How a New Policy Let to Seven Deadly Drugs," *Los Angeles Times,* December 20, 2000.

[4] Ibid. Adverse events increased from 136,836 in 1993 to 258,125 in 1999.

make decisions: "The pressure to meet deadlines is enormous. The basic message is to approve."[5]

These goals force the agency to take an unvarying, "cookie cutter" approach to drug approvals. It is not in the public interest to require the FDA to act at the same speed for all standard or priority drugs and biologics. Some should get more time, some should receive less; time should not be the measurement of the agency's success. The agency has adequate tools to enable patients to obtain drugs before they are approved for marketing (as with the Treatment IND), so that desperately ill patients can have early access to potentially important medicines.

Moreover, it is completely inappropriate to give a regulated industry a dominant voice in determining what will be the process ("performance goals") for oversight of that industry. Congress established these goals in consultation with the prescription drug industry and received absolutely no input from consumers. The end result is that the regulated industry controls not only the funding and timeline for new drug approval, but the measurement tools that are used to determine the FDA's success or failure in this matter.

PDUFA allows companies to manipulate the FDA into quickly approving drugs that the agency has not had adequate time to review. Companies can do this simply by dragging their feet in submitting required data and test results until the FDA's "performance" deadline draws closer. If this practice is used on a regular basis, it puts the FDA under tremendous time pressure to meet its performance goals without adequately reviewing the submitted data. In other words, the FDA's performance goals, which are based on the agency's ability to meet many decision-making deadlines over the course of time, may actually provide companies with an incentive to delay transmitting some data to the FDA quickly. If they give the FDA the information "too early," the agency might actually have more time to find flaws in the information.

3. PDUFA is draining resources from other critically important FDA public health functions, such as monitoring the safety of drugs once they are on the market and approving generic drugs for entry into the market. This distorts the overall priorities of the agency. The pharmaceutical industry insisted that a large, inflation-adjusted portion of drug review costs be funded through appropriations. Congressional budget increases to the FDA have not kept up with the mandated spending increases in PDUFA. According to the FDA, it has had to absorb $284 million in unfunded pay raises and other inflationary costs in the last eight years.[6] To his credit, the President has proposed funding in his budget to catch-up on these expenses.

Here's what the FDA has to say about the impact of PDUFA on the rest of their mission: "We are increasingly concerned that spending enough appropriations on the drug review process to meet the statutory conditions makes the FDA less able to manage the resources available in a way that best protects the public health and merits public confidence."[7] Former Commissioner Jane Henney went a step further, "...the truth is, the program is barely surviving because of the way it was designed. We don't have the resources to do the things we believe are essential, such as adverse event reporting, because they are not supported by PDUFA funds."[8]

Moreover, the director of FDA's Center for Drug Evaluation and Research, Janet Woodcock, has expressed a great deal of concern about FDA staff turnover, and ultimately, their experience and competency. She has said that the intense timelines under PDUFA have created a "sweatshop environment that's causing high staffing turnover."[9] Many of the FDA's most highly trained scientists and experts are leaving within three years, preventing the agency from building an institutional memory of previous reviews.

One of the areas of FDA's work that is suffering from a dramatic lack of resources in the post-FDAMA and -PDUFA era is oversight of prescription drug advertising to consumers. As the number of drugs approved has increased, so has industry spending to promote these drugs. Since 1997, pharmaceutical industry spending on direct-to-consumer advertising has skyrocketed: increasing by 42 percent between 1996 and 1997, by 23 percent between 1997 and 1998, and by 40 percent between 1998 and 1999. In 1999, drug companies spent more than $1.8 billion on direct-to-consumer advertising.

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[5] Ibid.

[6] FDA Talk Paper, April 9, 2001

[7] Food and Drug Administration, "PDUFA Background Information," FDA, August 2000.

[8] FDA Consumer Magazine, "User Fees for Faster Drug Review: Are They Helping or Hurting the Public Health?," September-October 2000.

[9] Ibid.

The FDA staff responsible for reviewing these promotional materials has not increased proportionately. FDA has only 13 people responsible for primary review of the 32,000 pieces of promotional material that the agency receives in a year. This level of resource commitment is clearly insufficient to enable FDA to act promptly on violations of the requirement that ads be accurate and include a fair balance of information about risks as well as benefits. Slow action on inaccurate and incomplete advertisements is a serious problem for consumers. Until the agency informs a company that it must withdraw or change an ad, the public will continue to be exposed to false information and to ads that fail to include important risk information. Delays in this area pose an unacceptable threat to the public health.

4. PDUFA does not prioritize between speedy approval of drugs that are truly important and those that represent no therapeutic advancement. Unfortunately, the FDA's regulatory process as defined by statute and regulation does not provide it the latitude to prioritize the new drug approval process based on a ranking of medical and public health needs. The FDA has four categories for approval of new drugs: (1) Those for serious or life-threatening conditions for which there is no adequate treatment; (2) drugs for rare disorders; (3) the majority of new drugs that are approved, which are redundant chemical modification of drugs already marketed; and (4) drugs that are granted priority review because they work in some new way.

We suggest that drugs that fall into the third category above, such as a drug for erectile dysfunction, or the third or fourth cox-2 inhibitor, do not need to be rushed to market as quickly as an important new anti-cancer agent or an enzyme replacement therapy for a genetic disease. Many new drugs that have appeared on the market as a result of the agency's PDUFA enhanced approval resources, may actually turn out to provide little, if any, benefit to patients when compared to older, better-understood and often less expensive predecessor drugs.

5. The best way to insure the timely approval of safe drugs is to adequately fund the FDA from general revenues. Adherence to this principle would be the surest way to remove the worrisome potential for conflict-of-interest that arises when dedicated income streams flow to the regulator from the regulated industry. If Congress continues to underfund the FDA, it will be essential for Congress and the agency to establish better procedures and guidelines to prevent the serious conflict-of-interest concerns that our organizations have raised in this testimony.

PEDIATRIC EXCLUSIVITY

FDAMA granted drug companies a six-month patent extension if they conduct pediatric testing on a particular drug. This provision expires in January of next year. The Patient and Consumer Coalition agrees with the FDA that the pediatric exclusivity provision "has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling."[10] As a result, we support renewing this provision.

However, Congress should enact measures to make pediatric exclusivity more targeted and effective. Pediatric exclusivity has delayed the introduction of more affordable generic alternatives on some very important and widely used drugs and has proven to be very lucrative for brand drug companies. But it has not yet resulted in the testing and labeling of some of the most widely used pediatric drugs. Six of the ten drugs without adequate labeling for children are not eligible for pediatric exclusivity because they are off-patent. For example, dopamine hydrochloride, which is used to stabilize the blood pressure of sick babies, has never been formally tested in children. Moreover, the exclusivity applies to every formulation of a drug, even if only one formulation is tested.

We recommend that Congress consider a number of possible measures that could make pediatric exclusivity more effective and less costly, while still providing an incentive for brand companies to test. Our coalition has not formally endorsed any of these proposals yet, but we urge Congress, as we are, to seriously consider each of them. These measures could include: tax credits to encourage companies to conduct studies on drugs that are off-patent; making funds available to the Centers for Education and Research on Therapeutics (CERT) sites and the Pediatric Pharmacology Research Units to do testing of drugs that are off-patent; allowing exclusivity only on the particular formulation of a drug that is tested, and not on others in that line that will not be offered to children; scaling the length of exclusivity to the sales of a drug, so that Americans would not have to pay higher prices on blockbuster drugs

[10] Department of Health and Human Services, U.S. Food and Drug Administration, "The Pediatric Exclusivity Provision, January 2001, Status Report to Congress."

that recoup the cost of pediatric testing in far less than six months; directly linking the granting of exclusivity to a company making labeling changes, and codifying the FDA's authority to require companies to test new drugs on children. Congress should also insist that the FDA retain bioethicists to review all proposed pediatric clinical trials in order to ensure that the agency gives appropriate consideration to the ethical concerns that come up around the possibility of exposing children to unnecessary and sometimes dangerous risks in clinical trials.

In conclusion, let me say that Congress will consider no legislation this year that is more important to this nation's safety and health. As a result of the serious problems that I have noted with the Prescription Drug User Fee Act, what is at stake is nothing less than public trust in the nation's drug safety system. Right now, Americans have every reason to wonder if the FDA can really protect them. We urge this committee to act quickly to eliminate conflicts-of-interest in PDUFA, prevent the drug industry from dictating the timeline and standards for drug approval and properly fund *all* FDA drug monitoring and approval functions—not just new drug approval. It is time to refocus the FDA's attention on its real customers: the American people.

Thank you again for the opportunity to offer our comments.

Mr. BILIRAKIS. Thank you, Mr. Plunket.

Dr. Franson?

STATEMENT OF TIMOTHY R. FRANSON

Mr. FRANSON. Thank you very much. Good day, Mr. Chair and members. I am Tim Franson. I am a physician, a pharmacist, and Vice President of Clinical Research and Regulatory Affairs at Lilly. On behalf of PhRMA I want to thank you in particular, Mr. Chair, for the vital role you and this subcommittee played in helping to enact the 1997 Food and Drug Modernization Act.

The bottom line of my testimony today is this. FDAMA is working. It is working just as Congress intended, and it is for the benefit of patients.

My written testimony, which I wish to submit for the record, sets forth the FDAMA provisions that directly affect our industry, and outlines our views on some of these provisions. Clearly many parts of FDAMA were expected to be, and are, implemented over a period of years. We continue to work with FDA to ensure that the full potential of these provisions is realized.

I would like to turn to one of the most significant programs established by the 1997 law, the Better Pharmaceuticals for Children Act, legislation sponsored by Representatives Greenwood, Waxman, and Burr. This act has dramatically improved all aspects of pediatric drug development. It changed the way FDA manages pediatric drugs, prompting the agency to establish a dedicated group of individuals who focus on drugs for children. It also changed the way our industry approaches pediatric drug development and pediatric studies. That law sent a loud and clear message from Congress. We want our commitment to children to be reflected in the development of more drugs for children.

The pediatric research incentive has meant that pediatric patients are now standing on equal terms with adults in the stiff competition for research dollars at our companies. Our industry shares the view FDA expressed in its report to Congress about the pediatric program. The program, the agency said, "has been highly effective for many drugs." The response of the pharmaceutical industry "has been vigorous."

Our response has been motivated by commitment to improving children's health, not only by focus on products with high commer-

cial yield. In fact, when one looks at the list of most frequently prescribed drugs, as published by Pharmacy Times, over half of the medications being studied for pediatric information are outside the top 100 drugs used. The results of the program speak for themselves. As you have already heard to date, FDA has issued 188 written requests, inclusive of over 400 pediatric studies, many of which are ongoing.

We also recognize, as FDA and others have suggested, that some changes might make the program even better. In particular, we agree with FDA and the American Academy of Pediatrics that a different approach is needed to produce pediatric studies and revise labeling for older drugs whose patents have expired, and for which the pediatric research incentive does not work.

We also agree with FDA that it is not necessary to continue to exempt pediatric supplemental applications from the requirement to pay user fees under the prescription drug user fee program. Such pediatric supplemental user fees we know will help FDA to expand its efforts in this important area. Most importantly, will help to ensure that pediatricians and children realize the benefits of this important initiative as quickly and as efficiently as possible.

We strongly urge you, Mr. Chairman, to reauthorize the Better Pharmaceuticals for Children Act. We also strongly urge that you determine about any proposal to change the program whether it will help children. We urge you to reject any change that will not promote the goal of providing better pharmaceuticals for our children.

Accompanying me today to answer any questions you may have on the pediatric research incentive program is Dr. Stephen Spielberg, a pediatrician, a pediatric clinical pharmacologist, and Vice President of the Drug Development at Janssen Research Foundation.

Finally, Mr. Chairman, I want to talk briefly about the other FDAMA program that will expire, the Prescription Drug User Fee Act, PDUFA. Let me simply say that PDUFA has provided FDA with necessary funds to hire additional reviewers, update the agency's information technology infrastructure, and act in a more timely and predictable manner on drug applications. It has been highly successful for FDA, for our research-based industry, and especially for patients.

PDUFA must be renewed in 2002 to provide continuity for FDA, and ensure that patients continue to receive safe and effective new medicines as expeditiously as possible.

Thank you very much for the opportunity to testify. I will be pleased to answer any questions you have.

[The prepared statement of Timothy R. Franson follows:]

PREPARED STATEMENT OF TIMOTHY R. FRANSON, VICE PRESIDENT, CLINICAL RESEARCH & REGULATORY AFFAIRS, LILLY RESEARCH LABORATORIES, ELI LILLY AND COMPANY ON BEHALF OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Mr. Chairman and Members of the Subcommittee: I am Dr. Timothy R. Franson, Vice President of Clinical Research & Regulatory Affairs at Eli Lilly and Company, and I am here today on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to present the industry's views on the implementation of the Food and Drug Administration Modernization Act (FDAMA) of 1997, a landmark law that marked significant progress for public health and patients. PhRMA rep-

resents the nation's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing new life-saving, cost-effective medicines.

As the Chairman and other Members of the Subcommittee well know, FDAMA was the first substantive modification to the pharmaceutical provisions of the Federal Food, Drug and Cosmetic Act in more than 30 years. It reauthorized the successful provisions of the Prescription Drug User Fee Act (PDUFA) of 1992, which provided, through the collection of industry user fees, necessary additional resources for FDA to use in reviewing new drugs. Next year, this Subcommittee will need to look into reauthorizing PDUFA. The user-fee law has produced many critical improvements at FDA since it was first enacted in 1992 and, in particular, has enabled the agency to develop a more efficient review process that has given patients more timely access to new medicines. PhRMA looks forward to working with the Subcommittee in this endeavor.

Another important provision of FDAMA was the Better Pharmaceuticals for Children Act (Section 111), legislation sponsored by Representatives Greenwood and Waxman, which provides an incentive to industry to develop specific information about pediatric uses of prescription drugs. This latter provision should be reauthorized before it sunsets at the end of this year—for the health of our children.

Collectively, the reauthorization of PDUFA and other important structural changes made by FDAMA in FDA procedures have shortened the FDA review process for New Drug Applications (NDAs) and thus made safe and effective new drugs available sooner to patients. FDA review is the final and critical step in a drug-development program that begins many years before the submission of an NDA or, for a biological product, a Biologics License Application (BLA), and includes the human clinical trials for which a company has filed an earlier application with FDA.

The bottom line of my testimony today is this: FDAMA is working just as Congress intended for the benefit of patients. The 1997 law has promoted increasingly efficient and effective working relationships between FDA and patients, doctors, and regulated industries; increasingly productive communications between FDA and its many constituencies, including our research-based pharmaceutical industry; sorely-needed improvements in FDA's information technology; and—most significantly and importantly—speedier access for patients both to safe and more effective new products and to experimental medicines still in clinical testing.

Clearly, many parts of FDAMA were expected to be—and are being—implemented over a period of years. We continue to work with FDA to ensure that the full potential of these provisions is realized. We also recognize that, because the number of applications for new products is increasing, FDA's workload is growing, and the agency's priorities must be focused on these applications.

With that as an overview of our overall evaluation of FDAMA implementation, I would like to turn to one of the most significant programs established by the 1997 law—the Better Pharmaceuticals for Children Act.

For a number of years prior to enactment of FDAMA, FDA and pediatricians had attempted several times to spur the development of drugs for pediatric patients and to increase the labeling on products used for children by encouraging more pediatric studies to be conducted. Notwithstanding these efforts, many medicines continued to be used for children without adequate labeling information for pediatricians and parents. The pediatric provisions of FDAMA have dramatically improved that situation. They changed the way FDA manages pediatric drugs, prompting the agency to establish a dedicated group of individuals who focus on drugs for children. They also changed the way our industry approaches pediatric drug development and pediatric studies.

Before enactment of the Better Pharmaceuticals for Children Act, pediatric drug development was often slighted in competition with other company R&D projects for necessarily limited resources. Because of the difficulty of conducting clinical studies with children and the substantial additional risks of such clinical programs, R&D directors often preferred to focus their limited resources on drug-development programs for adults.

Thanks to you and FDAMA, a company R&D director today can weigh the substantial cost of pediatric drug development against the incentive you provided in FDAMA. That law sent a loud and clear message from Congress—we want our commitment to children to be reflected in the development of more drugs for children.

The FDAMA incentive has meant that kids are now standing on equal terms with adults in the stiff competition for research dollars at our companies. FDAMA is changing the world for pediatricians who prescribe drugs for children, for parents who administer these drugs, and, most of all, for the children themselves.

The statistics speak for themselves. As of April 2001 companies have proposed to study 218 medicines. This represents a remarkable increase in interest in conducting pediatric studies. With suggestions from professional organizations, such as

the American Academy of Pediatrics, industry, and the public, FDA has issued 188 written requests for pediatric studies and 411 such studies have actually been initiated. Twenty-eight drugs have received six months of exclusivity under the 1997 law, and new pediatric labeling has been provided for 18 of these products. Additional label changes will be made as FDA completes its review of the data from all of the studies.

So far, the completed and ongoing studies have resulted in the development of new formulations to cover additional and younger patients and the development of novel clinical trial designs and tools to evaluate safety and effectiveness. Requests for studies have been made for drugs in a wide range of therapeutic areas, from common problems such as treatment of fever, skin infections, and pain to cardiac disease, endocrine problems, gastrointestinal disorders, serious infections including HIV, seizure, and other neurologic disorders. Studies have involved pediatric patients of all ages.

The range of conditions addressed, the variety of drugs being studied, and the nature of the scientific data requested all show that FDAMA is successfully addressing unmet therapeutic needs in children. No other approach, legislative or regulatory, has ever had such a profound impact on the development and evaluation of medicines for children.

Why has this legislation worked so well when other approaches for more than 20 years have invariably failed?

The legislation has been such a success because it addresses the fundamental impediments that have hampered the conduct of pediatric studies of drugs in the past—principally the small number of pediatric patients. Fortunately, most children are healthy. In the adult population, there are large numbers of patients with diseases such as heart disease and cancer who are available for clinical trials and who constitute a large market for medicines to treat those diseases. By contrast, with pediatric patients, serious and chronic illness is caused by a wide range of diseases, but relatively few children are affected by any particular disease. For example, fewer than 0.5 percent of patients with arthritis are children, and juvenile rheumatoid arthritis is a different disease than adult rheumatoid arthritis or osteoarthritis.

The limited patient population has several consequences. First, clinical trials are inherently more difficult to conduct with children than with adults. The trials are much smaller because relatively few children have a given condition. The children are of different ages. As a result, they may need different, age-appropriate formulations of medicines for accurate and compliant administration. For example, an oral liquid may be needed for young children (sometimes different concentrations for newborns), while chewable tablets may be required for somewhat older children still unable to swallow pills or capsules.

Further, the pharmacokinetics of drugs (i.e., the rate at which they are absorbed) varies widely with age. In addition, age-specific study designs to assess effectiveness and safety may be needed. Studies are particularly complex in tiny premature infants who may weigh less than a pound. These babies are among the sickest groups of children.

Added to these complicated technical, scientific, ethical, and medical issues are unique regulatory requirements. Sometimes, a development program for pediatric drugs must include the duplication of an entire clinical program for each of the pediatric age categories for which an indication is sought. For example, if the clinical development program included adults 16 years of age and older and the sponsor wishes to investigate safety and efficacy in children 12 to 16, tolerance studies may be required.

These tests can be followed by bioavailability and finally safety and efficacy studies in children with the disease. If the sponsor then chooses to seek the indication in children ages 6 to 12, the initial studies would again be tolerance studies followed by bioavailabilty tests before the safety and efficacy studies could begin. This process would continue for the age groups below 6 years of age—i.e., 3 to 6, 1 to 3, 6 months to 1 year, and less than 6 months.

It is evident, therefore, that a clinical development program necessary to address all age groups for children can be much more extensive than a development program needed to address the age group 16 to 65. And, once formulations are produced and validated, studies are performed, regulatory hurdles are met, and labeling ultimately is changed, the market for most medications for children is very limited.

In general, the research-based pharmaceutical industry shares the view FDA itself expressed in its January 2001 report to Congress about this program. The program, FDA said, "has been highly effective for many drugs" and the response of the pharmaceutical industry "has been vigorous." Our response has been motivated by a commitment to improving children's health, not by a focus on products with high

commercial yield. In fact, when one looks at the list of most frequently prescribed drugs published by Pharmacy Times, over half of medications being studied for pediatric information are outside the top 100 drugs used.

We also recognize, as FDA and others have suggested, that some changes might make the program even better. In particular, we agree with FDA and the American Academy of Pediatrics that a different approach is needed to address the issue of how to achieve pediatric studies and revised labeling for older drugs without remaining patent life, for which the exclusivity incentive does not apply. We have been discussing this matter extensively with the AAP and look forward to working with you to ensure that this issue is addressed appropriately.

We also agree with FDA that in general it is not necessary to continue to exempt pediatric supplemental applications from paying user fees under the Prescription Drug User Fee program. Such pediatric supplement user fees, we know, will help FDA expand its focus on this important area and—most importantly—will help ensure that pediatricians and FDA resources for children realize the benefits of this important initiative as quickly and efficiently as possible.

Several points should be emphasized in considering the vital need to reauthorize the Better Pharmaceuticals for Children Act this year:

(1) Regardless of other aspects of health economics and health-care financing, the small number of pediatric patients with a specific disease available for study, the complexity of the studies, and the ultimate limited market for pediatric drugs will remain. If resources are constrained at any time for any reason, research on the therapeutic needs of children is at risk. It is crucial to keep the medical needs of children competitive with the medical needs of adults in the scramble to obtain company research funds. Section 111 makes that possible.

(2) The Better Pharmaceuticals for Children Act remains a critical stimulus to study unique pediatric diseases and indications. Many pediatric diseases differ significantly from those in adults and FDA's Pediatric Rule thus does not apply. This is particularly the case for diseases in premature neonates. The pediatric program is the best mechanism to ensure that the unique therapeutic needs of children are met.

(3) Section 111 encourages companies to initiate studies in a timely manner. With the incentive in effect, companies are more likely to initiate studies earlier in the drug development process rather than seek to defer the tests. Pediatric studies should not delay the development of important new therapies for adults. As more advanced and novel therapies are developed, the pediatric program can ensure that children fully benefit from these developments.

(4) Because of technical oversights in the drafting of FDAMA, antibiotics are ineligible for the exclusivity provisions of Section 111. Since many of these drugs are likely to have significant clinical benefits for children, Congress should ensure they are covered when the pediatric provisions are reauthorized.

(5) There has been significant variation in interpreting the legislation and implementing written requests among FDA review divisions. Much of this is understandable with a major new initiative. Often, disease definitions, extrapolation of disease similarity, and thus the nature of the requests have been inconsistent. Sometimes, this has been caused by a lack of understanding of pediatric diseases, sometimes by a lack of pediatric expertise in FDA review divisions.

(6) Where inconsistencies have arisen, consensus approaches have been developed through the Pediatric Advisory Subcommittee, together with the American Academy of Pediatrics, the National Institute for Child Health and Human Development (NICHD, and its Pediatric Pharmacology Research Units, the PPRUs), other National Institute of Health (NIH) institutes including the National Cancer Institute (NCI), and parent/patient groups. All parties have learned to focus on the therapeutic needs of children and work to achieve consensus. This has been a major unanticipated benefit of the legislation. The cooperative process also has helped to address several issues in the area of pediatric cancer.

FDA has formed a new Pediatric Oncology Advisory Subcommittee, and prepared guidelines in the area of pediatric oncology. PhRMA has created a Pediatric Oncology Task Force. These groups are working together with the Children's Oncology Group and NCI. Recognizing that many areas of medical and scientific complexity now being addressed need to be resolved, FDA should act to achieve consistency among review divisions, based on the best pediatric and pharmaceutical science.

Further, FDA needs increased pediatric resources to deal with these issues. Such resources must include more personnel with detailed knowledge and expertise in pediatric investigation. To the extent that some of these matters can be addressed by increased FDA resources, user fees could be a mechanism.

PhRMA supports the elimination of the current pediatric supplement exemption under PDUFA, to help achieve the goals of the pediatric provisions.

(7) While Section 111 is working to meet the needs of children, the incentives may not be able to overcome the barriers to very early initiation of pediatric studies for truly life-threatening but very rare conditions, such as certain pediatric cancers. There is substantial risk and difficulty in conducting pediatric studies for new chemical entities under development for large adult populations, given the rarity of some of these conditions in children. As we approach the renewal date for the Better Pharmaceuticals for Children Act, we urge this Subcommittee and Congress to consider how to improve the climate for early initiation of pediatric studies. We would, of course, be pleased to work with you and others who share these concerns.

Another area that is important, though not directly related to this program under FDAMA, is the obvious limitation in clinical investigative resources for pediatrics. This deficiency has become increasingly apparent. The creation of the NICHD-sponsored PPRUs has been a major advance. It is critical that pediatric studies be carried out at centers with extensive pediatric expertise. The safety and welfare of research participants and the validity of the data generated are dependent on the expertise of the centers at which studies are conducted.

PhRMA strongly supports additional new legislation to encourage the training of the next generation of pediatric clinical pharmacologists, by providing training funds to the PPRUs and debt forgiveness for trainees who enter careers in pediatric drug development. Such a program would develop a pool of talent available to academic medical centers, industry, and FDA to ensure that advances in therapeutics can be translated into medicines for children. As the Subcommittee considers additional ways to advance the health and well being of children, we would be pleased to discuss further how to increase the cadre of skilled, trained, and committed pediatric researchers.

In sum, the success of the Section 111 suggests that the current incentive is reasonable. But the value of the program in adding clinically meaningful pediatric information to package inserts is still in its infancy. Because of the brief amount of time during which applications could be submitted to date (the five-year program could not really begin until FDA developed a list of relevant drugs (which took more than a year), many drug sponsors focused only on the products that could be studied during this relatively short implementation period. Much more needs to be done.

PhRMA strongly urges Congress to reauthorize the Better Pharmaceuticals for Children Act. The task has just begun of studying and labeling currently marketed medications for children. The increasing rate of industry study proposals and written requests for studies by FDA shows continuing progress, which would be slowed and then stopped if Section 111 were allowed to expire.

I would like to address our second major point—implementation of other FDAMA pharmaceutical provisions. As has been stated, the overriding goal of Congress, FDA, patients, and industry in working cooperatively to enact FDAMA, was to ensure that safe and effective new medicines would be made available to patients as quickly as reasonably possible. This is occurring without any compromise in FDA's high safety standards.

In fact, nothing in either FDAMA or the original 1992 user-fee law lowered the agency's high standards. FDA has long been the worldwide gold standard of drug review and approval. That standard is being preserved and, indeed, enhanced. But now, thanks to FDAMA and PDUFA, many critically important new drugs are being approved in the U.S. earlier than in foreign countries—a real reversal from a decade ago.

To those who argue that FDA is moving too fast in approving new drugs, PhRMA suggests that they examine the record. Nothing is more valuable to our industry and our companies than the safety of their products—primarily for their patients, but also for their long-term reputations for trust, integrity, and reliability. Some argue that the withdrawal of six drugs from the market over the past five years should trigger a sharp change in policy. But consider that a record number of 184 new molecular entities were approved during this period. As a result, the percentage of drug withdrawals compared to new-drug approvals is consistent with historical averages. Moreover, the reduction in the net drug-approval time by half since the first user-fee law was enacted means that patients have earlier access to the new and better treatments they need.

There were a number of FDAMA provisions aimed at improving the drug review and approval process. Most of the provisions were designed to improve FDA processes, but some also were directed at industry. All of the provisions were the result of extensive dialogue between the Congress, FDA, industry, and the public.

The progress made by FDA to date in implementing FDAMA has been steady. Most of the guidances required by FDAMA have been completed. We have provided a list attached to this testimony that notes each FDAMA initiative that addresses drug regulation or FDA management that relates to our products. It appears that most of the initiates are being implemented effectively and efficiently. In some cases, it is either too early to make an assessment or sufficient data have not been collected to evaluate the situation.

Mr. Chairman, that concludes my written testimony.

Mr. BILIRAKIS. Thank you very much, Dr. Franson. The Chair now yields to Mr. Burr to inquire. You can take your full 5 minutes if you like.

Mr. BURR. Mr. Chairman, it will not take me 5 minutes. I really just have a statement and a question. I appreciate the Chair's indulgence, to try to meet a school group.

I see Mr. Shuren here from the FDA. Let me ask, are you the only representative from the FDA still in the audience?

Mr. SHUREN. I believe I am.

Mr. BURR. And your role at the FDA is what?

Mr. SHUREN. I am a medical officer.

Mr. BURR. Let me suggest to you, and I will request of the Chair and the ranking member, that we send a letter to the FDA once again stating that they have missed a great opportunity for their policy folks who were here to testify to stay and listen to the experts. I think that it is a missed opportunity once again. I hope this is an agency that will learn if we push it a little bit harder. I hope you will personally carry the message back. I know that everybody has a hectic schedule, but there is no greater opportunity than to listen to the same people that we feel are the experts on these issues who are willing to come and testify. It certainly saves you time in the long run. I hope you'll carry it back.

Mr. BILIRAKIS. Your point is well taken.

Mr. BURR. My question is to Ms. Ben-Maimon, is that correct? Let me ask you. You said that you had three children.

Ms. BEN-MAIMON. I do.

Mr. BURR. If one of your children were seriously ill, and the doctor said to you "I can provide an ability for your child to live for an additional 70 years, but it will cost your life," what would you do?

Ms. BEN-MAIMON. Obviously I would give my life for my child's, without any question.

Mr. BURR. If the promise were only for 20 years, what would you do?

Ms. BEN-MAIMON. Again, there is not any question.

Mr. BURR. If the promise were for 1 day, what would you do?

Ms. BEN-MAIMON. I would probably make the same decision.

Mr. BURR. I thank you for answering that question.

Mr. Chairman, I yield back.

Ms. BEN-MAIMON. Can I respond though as a physician? Clearly those are not the kinds of decisions that we need to make. We need to make decisions where we measure benefits and risks. I have been in the drug industry both in the proprietary side and on the generic side for almost 10 years, I guess, and I have treated patients.

Mr. BURR. Ms. Ben-Maimon, let me say this. There are doctors to your right. There are doctors to your left. The one thing I have

learned about doctors is that each one has a response. It may be a little bit different. There is not going to be consensus. There is a parent in every row. Parents will answer that question exactly like you did. If our concentration is on children, then let's stay focused on children. If there is a remote chance at whatever cost that we can save the lives of children, then do we not have a responsibility to do it?

Ms. BEN-MAIMON. Not if that is not our only choice, because I think we can save the lives of children while still improving the lives of others. We should try and do that before we make a sacrifice we may not necessarily need to make.

Mr. BURR. I'll let the pediatricians battle that one with you.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. The Chair yields to Mr. Brown to inquire.

Mr. BROWN. Thanks, Chairman.

I'm glad to hear that my friend, Mr. Burr, with whom we've worked together on a variety of issues, is now going to vote against the President's tax cut and put more money into child prevention and other programs that will help America's children.

Mr. BURR. The gentleman has to realize that the choice is to leave that money here and let us spend it. I would much rather get it out of town.

Mr. BROWN. That estate tax break is going to save a lot of children's lives.

Prozac about 6 months ago or some time ago got a 6-month exclusivity estimated to be worth around $2 billion to the manufacturer. Prilosec, a very important drug, largest selling drug in America, estimated sales of $4 billion in the year 2000. It's an important drug for children. Astra Pharmaceuticals recently did pediatric studies on the drug. This week they got 6 months of exclusivity for doing so.

This question will be to all six of you. The 6 months of exclusivity without generic competition for Prilosec for Astra Pharmaceuticals is estimated to be worth about $1.2 billion in additional profit. The President's budget, squeezed by the tax cut, I might add, for the entire National Institute of Child Health and Human Development for the coming year is $1.1 billion. So Astra for the 6 month extension will get $1.2 billion in additional profit. The President's entire budget for the NIH Child Health and Human Development is $1.1 billion total. To be sure, Prilosec is a good effective important drug. Can each of you honestly, or any of you honestly tell me that the one pediatric trial that Astra is doing is worth more than all the NICHD budget together, combined?

Mr. KEARNS. The simple answer is no. I don't think it is worth more than the budget.

There is an incredibly difficult conundrum for those of us who do pediatric research and care for children. That is, we have been for so many years without an avenue to include kids, that most of the work that was done was done out of people's pockets, meaning academics, schools, medical schools, pharmacy schools and the like. So now with FDAMA and the pediatric provision, the avenue to include kids is there.

I must say and confess that when it comes to the issue of profitability, I really put my head in the sand many times because of the

zeal to do what's right by kids. I am an NIH-funded investigator. I would love for part of that money to go to NICHD. It could further improve what we do. Unfortunately, I don't have a simple solution. The Astra drug is an important drug for children. It improves the lives of many kids and many families, but is it worth the NICHD budget? In my personal estimation, no.

Mr. BROWN. Dr. Ben-Maimon?

Ms. BEN-MAIMON. I would like to keep my remarks brief because again, I want to reiterate that we actually do support the concept. The concern I have again as a physician, primarily, is that sums that large can actually make the incentive, turn the incentive into a mechanism to exploit. We want to encourage children and the study in children, but we want to be sure that we do it and protect them, and make sure that we do it when we really need to be doing the research. So again, I would challenge Congress and ask them as they reauthorize the pediatric exclusivity provision, that they consider what is the appropriate incentive to ensure these studies continue, yet that we do it in a way that we don't encourage companies to exploit our kids.

Mr. BROWN. Dr. Gorman?

Mr. GORMAN. The 6 month's exclusivity is a broad brush painted across many drugs. While in the case that you present it has become extraordinarily profitable for a single company, it has also prompted the development of knowledge in other drugs that are not nearly so profitable.

My favorite example on the list of labelling changes already is Lacthydrine, which is not on anybody's top 200 list, and is a cream use for ichthyosis, which is a disease I hope no one in this room has heard of. It was also incentivized under this program.

The simple answer to your question again is no. I don't think that one drug company needs to profit to the extent of the increased NICHD budget. On the other hand, the information made available to children today from that study will be available for the next 100 years. The profitability will be gone for 99.5 years after that.

Mr. BROWN. As I might add would direct government—if the government did the study directly the same information would be there, I would add.

Ms. Meyers?

Ms. MEYERS. Mr. Brown, I have three children who have a rare disease. They are adults now. I have been saved by drugs. But all three have participated in clinical trials. Now I have six grandchildren. I want pediatric studies to be done for the sake of my grandchildren. I am very proud to say that my adult children all did participate when they were children. But when my 85-year-old mother can't pay for her drugs when she goes to the drugstore to pick them up, she calls me and asks me to pay for them. So I feel particularly torn by this problem, asking my 85-year-old mother who can't afford her drugs, to pay for her great-grandchildren. I don't think that it is fair. I think it is Congress' responsibility to make it fair.

Mr. BROWN. Mr. Plunket?

Mr. PLUNKETT. I will just add that our coalition does support the exclusivity, but we think it has to be more targeted, more effective

and less costly. We shouldn't have to make this tradeoff, cost versus testing for kids. In our testimony, we have a range of possibilities we would urge the committee to explore to make it more targeted and more effective because the way that it is written now, it does increase costs for consumers. That's not acceptable, especially on important drugs like the ones you have mentioned. It shouldn't happen.

I think that this committee has a range of options it can consider, from tax cuts to scaling the exclusivity based on the sales of the drug, to a number of other ideas that can make this provision more targeted and more effective.

Mr. FRANSON. In response to your question you had mentioned several compounds. I think it is important to note that any time we look at drug studies in pediatrics, they have both short-term impact and long-term.

In the case of these for exclusivity, you mentioned both Prilosec and I believe Prozac, both of those are used for a broad range of problems significant in pediatrics. Both required at least some, if not a broad range of studies. In the near term, met important clinical needs.

In the longer term, I think one of the tremendous benefits of FDAMA and the pediatric incentives has been that it has created or reignited the excitement for an infrastructure for doing pediatric clinical studies and research. That was not present previously broadly in the United States. This has been a wonderful benefit that will serve the public health long-term.

Second, it has allowed companies such as ours to reinvest some of that that has been gained through exclusivity to actually begin new programs and lines of drug research devoted exclusively to pediatrics. I think the benefit of that balanced against the cost long-term would be difficult to project, but it is not inconsequential. I would suggest that those kind of benefits need to be weighed in that are very significant.

Mr. BROWN. I would add one sentence if I could, Mr. Chairman. The high end estimate of how much it costs a company to do pediatric studies is $4 million a day. That is the extravagantly high end estimate.

Mr. FRANSON. A day?

Mr. BROWN. For the price of Prilosec's exclusivity, we could fund NIH to do 300 of the most expensive trials or some larger number obviously of less expensive.

Mr. BILIRAKIS. The gentleman's time has expired.

Ms. Meyers, I think you said it all when you made the statement, "I am torn." That is really what it comes down to here. Everybody has sort of agreed that FDAMA is working. Some people have indicated there are weaknesses and there should be changes made, but in general it's working. That is where we're torn too, because we don't want to take a chance on doing harm, as Mr. Greenwood indicated earlier in his opening statement. So that's really what we are faced with here. Obviously your testimony tears us even that much more.

I wanted to ask, Dr. Franson, a question on another subject, although it's pertinent to prescription drugs. Who determines the expiration dates on drugs?

Mr. FRANSON. The expiration dates on prescription drugs are determined by testing done by the company and then reviewed and validated with FDA.

Mr. BILIRAKIS. So both FDA and the companies determine the expiration dates?

Mr. FRANSON. We could not, for example, as an industry suggest a date that was not scientifically defensible and validated by a regulatory body.

Mr. BILIRAKIS. What about input from medical doctors regarding the expiration dates on the drugs and their efficacy?

Mr. KEARNS. It is really very difficult to answer that question, Mr. Chairman, because the data that was just spoken about is not generally available to the practitioner. For instance, if we knew that at the end of a 2-year period of expiration, for instance, that there was at least 90 percent potency there, I think few practitioners would have little heartache in using that drug. But if it was far less than that, especially for a drug with a narrow margin of safety, are you being used to treat a very difficult disease, it could be a real clinical issue. But again, it's the information is not available.

What drives the practice of medicine is a risk-benefit paradigm. Made in the absence of validated information, that becomes so difficult for physicians to do on a day-to-day basis.

Mr. BILIRAKIS. I appreciate that. If there's an expiration date, you as a physician are not going to prescribe that drug exceeding that expiration date.

Dr. Gorman?

Ms. Ben-Maimon, you are more than welcome to respond to it if you'd like.

Ms. BEN-MAIMON. I'll let Dr. Gorman comment first.

Mr. GORMAN. I think to echo that comment, there is very limited information on drugs being used past their expiration date. The only one that I'm presently aware of is tetracycline is really not good to use past its expiration date. Epicac, an over-the-counter drug that makes people vomit, works for 18 years after it is manufactured. After that, I am not aware of any information, would be hesitant to prescribe or recommend that patients use these drugs after their expiration date.

Ms. BEN-MAIMON. From the standpoint of industry, data is generated at room temperature for years out. The requirement is 90 percent. But of course it's sampled. You know, you are not testing every drug that's on the market. It assumes certain storage conditions. So drugs clearly are not intended to be prescribed after their expiration date. I think the cutoff is for most drugs, from a regulatory perspective, 90 percent. The problem is what happens in the marketplace and what happens if the temperature goes up over what the intended storage conditions are. Clearly the pharmacist is the one responsible, who should not be dispensing a product that is after its expiration date. Those products should be returned. So I don't think the pharmaceutical community would endorse administering these products at the end of their expiration.

Mr. BILIRAKIS. I appreciate that. I have visited a health clinic in Clearwater, Florida, that I have tried to help over the years, and seen half a dozen volunteers doing nothing but pulling drugs off of

the shelves that have been donated to them by physicians and throwing them into a container. There's all sorts of regulations in terms of how they have to dispose of these drugs. I see all that valuable time that these people volunteer spent pulling these drugs off these shelves. That's common place.

I have a problem with that. I realize of course that many of those drugs have exceeded their efficacious date. But I also suspect, and I'm not a physician, that in some cases these dates could be extended out. What about cases where people need drugs and it's either no drugs at all or else a drug which is at 90 percent efficacacy and can be available to help? That is the big question I have in my mind. I have talked to staff about it over the years. We can't seem to get much help or much of an answer.

Ms. BEN-MAIMON. I think the only way is to retest. I mean what happens is the data really is generated in real time. There are products that are retested. You know, if it's past its expiration date, drug companies do pull product or use other data to support it. So the only way that I think you could comfortably prescribe those products and tell patients to take it is if you retested them.

Mr. BILIRAKIS. My time has expired. But if any of you have any comments or thoughts on that subject, I would welcome receiving those.

Mr. Pallone?

Mr. PALLONE. Thank you, Mr. Chairman. During the testimony a number of suggestions were made. I guess most notably by Mr. Plunket, about possible measures that either as alternatives or that would make pediatric exclusivity more effective and less costly. I just wanted to look into some of those.

My question is to Dr. Franson. It occurs to me that a tax credit or a direct reimbursement program would be possibly more effective, efficient, and an equitable incentive than market exclusivity. If you think about direct reimbursements or credits, they would cover all products. They would be efficient since they would more closely reflect the cost of the test. They would be more equitable since the economic costs of the testing would be spread across a broader base rather than only on consumers of the product being tested.

I wanted to ask you whether PhRMA would support, for example, a three-for-one incentive in lieu of exclusivity. Would you be supportive of any of these measures?

Mr. FRANSON. I think we would be happy to assess and discuss and respond to the committee in whatever fashion to explicit proposals so we could understand that. I think the one thing that we remain committed to is that prior to FDAMA and the pediatric incentive, pediatric research was not being done. With the incentive, it is. We would want to carefully assess anything that was proposed to assure that we did not fall back to the prior state. So I could not commit or refute without more specifics, but would commit to you to provide a response.

Mr. PALLONE. Okay. But what about this idea of the three-for-one incentive? In other words, for every dollar you spend on a pediatric test requested by FDA, you would get either $3 cash or a triple tax credit? That's specific.

Mr. FRANSON. I think speaking as a physician and regulator, it is something I would be happy to refer back to my colleagues more sage in those kind of things and could provide a response.

Mr. PALLONE. That's fair.

Mr. SPIELBERG. If I might, I'm Stephen Spielberg. I am really speaking here as an advocate for pediatrics within industry. I am a pediatric pharmacologist who daily has to compete for resources for doing pediatric research.

The issue of the 6 month exclusivity is not on individual compounds. It's on our portfolio of compounds. When we look at the number of R&D dollars that I can attribute to pediatrics, it comes from exclusivity granted to very small drugs with very modest incomes, and to some very large drugs with very large incomes.

My ability to be able to compete for those funds and to assign those research dollars to children is dependent on indeed having those funds available as a result of the legislation.

Proof of the pudding is that it works. If you look at the first 28 drugs that have gone through the process, yes, two are in the top 10. Nine are not in the top 200. So that the larger items indeed support the lower items.

Mr. PALLONE. I appreciate that. I like the fact that Dr. Franson is willing to get back to me and maybe answer some of this.

I want to go one step further, if that's all right. If I could just ask one more thing, and then anybody who wants to. Let me just ask him one more thing and then if any of you want to comment, please.

This idea of—well, in her testimony, Dr. Ben-Maimon mentioned this Wall Street Journal article that estimated the cost of pediatric studies for pharmaceutical manufacturers to be between $200,000 and $3 million, which in turn the Journal says will increase drug sales by an additional $4 billion for the first 26 drugs tested. It says over 30 years, if the Wall Street Journal is accurate, pharmaceutical companies will make an additional $30 billion.

Now I just wanted to ask Dr. Franson again first, what is his view of this Journal estimate about how much pediatric studies cost the members of his association, and how much additional revenue they have earned. Second, because the companies themselves are the best source for providing the committee, since you are so willing to provide stuff, it would be helpful if you could forward information to us about the cost. In other words, the Wall Street Journal is saying something. I don't know if you agree with that, but you are obviously the best source for providing the committee with information as to how much the studies that have been completed already cost. If you could give us that kind of information, it certainly would be helpful as a follow-up.

Mr. FRANSON. Thank you. I would be happy to respond to that now. Regarding those figures, I believe those are quoted with the assumption that a single pediatric blood level, that is dosing study, could provide the basis for pediatric exclusivity.

Our understanding in discussions with FDA is that of all the drugs that have been provided a written request, none has only that as a facet. Therefore, that is a vast underestimate.

In many of the studies that have had pediatric requests filed, multiple studies of different diseases have been required for clinical

trials. Therefore, in addition to a pharmacokinetic or blood level study, there may be two studies required for a single indication or type of disease affliction, additional studies for more for that same drug. Therefore, the time and expense and skill necessary to complete those studies is significant. In the example of some we have had experience with, eventuated in over 22,000 pages of documentation submitted to FDA for pediatric exclusivity.

Mr. PALLONE. If you could just get back to us with regard to the three-for-one possibility or the tax credits, or maybe a critique of the Wall Street Journal, I would appreciate that. Any information you could provide us about whether it's accurate or what the real facts are.

Mr. FRANSON. It would be our pleasure. Thank you.

Mr. PALLONE. Thank you.

Ms. Meyers?

Ms. MEYERS. I would just say that a few months ago, FDA issued a statement saying that in the future all new drugs will have to be studied for children, so when they reach the market they will already be labeled for pediatrics. A number of PhRMA companies are suing the FDA to stop that. I would like to know why.

Mr. BUYER [presiding]. If you can answer the question, it's an open question. Questions come from the panel, not among the members who are sitting at the table.

The Chair now recognizes himself. To Dr. Tim Franson I will ask this question, Ms. Meyers, based on something I have read. In testimony you claim that performance goals contained within PDUFA created an incentive for drug companies to delay submission of data to the last moment, thus putting the FDA under tremendous pressure to meet the user fee deadlines. Do you see any evidence of this in your industry?

Mr. FRANSON. Regarding delays? If a company were to do something of that nature, to submit part of an application late after an initial application, there is actually a penalty imposed. That is called under FDA regulations at the Center for Drugs a major amendment. That would require the sponsor, the pharmaceutical company, to have a 90-day period of additional review granted to the FDA. So there would be no advantage for a sponsor to do something of that nature. It would be very important to the sponsor and to FDA to have sufficient time to review the substance of the information. So no, that is not our experience.

Mr. BUYER. Thank you. Has PDUFA led to higher percentage of drug recalls?

Mr. FRANSON. In the PDUFA period, I believe that the issues cited by FDA are correct. The withdrawal rate of 2 to 3 percent is accurate. In fact, I am personally surprised that it is not higher, given the vast number of drugs now introduced first in the United States as opposed to overseas. Of those 11 drugs that were cited, I believe four of those withdrawn drugs were actually approved before PDUFA. Therefore, it would be very difficult to ascribe a gap in the PDUFA review process when those drugs had already been on the market before that act.

Mr. BUYER. In January, the Clinton FDA report to the Congress stated that "PDUFA has been very successful." Do you see any reason to dispute that comment?

Mr. FRANSON. I would not dispute that.

Mr. BUYER. Thank you.

Doctor, how many of the 188 drugs examined under the pediatric exclusivity, how many of them were blockbuster drugs, are you aware of?

Mr. FRANSON. Regarding blockbuster, I'm not sure how everyone would define that. By the rankings——

Mr. BUYER. Over a billion dollars.

Mr. FRANSON. I believe I will ask my colleagues. Two of them may have been in that category. Is that correct?

Mr. SPIELBERG. Of the first group through, yes, that's right.

Mr. FRANSON. So two.

Mr. BUYER. Both the FDA pediatric exclusivity and Tufts University reports examined tremendous cost savings associated with pediatric exclusivity provisions. Do you believe that the pediatric exclusivity provisions may in fact save money in the long run? Do you believe that?

Mr. FRANSON. I would like to ask Dr. Spielberg to answer that.

Mr. SPIELBERG. Yes. I think in fact if you look at the FDA's report, when they deal with five conditions and only five conditions, they estimate savings by 25 percent decrease in the hospitalization of about $228 million a year. But that is only for five conditions. That is a modest estimate of the savings.

If I may point out two compounds that have been approved, Midazolam and Propofol. Both used for sedation in children in hospitals with new labellings and precaution. The most hazardous thing in pediatric hospitals is anesthesia and sedation for procedures, for example, a kidney biopsy or a liver biopsy. Getting proper information on dosing and precautions for those two medicines not only will decrease morbidity to those individual children, it will decrease hospital stays because the children will be properly sedated so the procedure can be done so you don't have to delay it until further medicines are administered. But it is going to decease the adverse effects of those medicines dramatically.

Mr. BUYER. Thank you.

The FDA tried more than 20 years to get the pharmaceutical industry to conduct pediatric testing, but none of their efforts succeeded until the pediatric exclusivity was passed. FDA reported in January that the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date. Why has the pediatric exclusivity proved so successful when other initiatives have failed?

Mr. FRANSON. I think Steve is an expert, would be best to——

Mr. SPIELBERG. I think again from my experience trying to encourage pediatric drug development, both on the academic side and now in industry, what it does is it fundamentally raises the priority of pediatric studies' allocation of R&D dollars, knowing that we have a reliable return on a compound, when that return can't be justified by pediatric sales and when we have very high risk in doing those pediatric studies, we don't know if we are going to get exclusivity. We don't know if we are going to get negative labelling, which should be in there for children if there is a negative effect.

That covers those issues, and therefore raises the priority of doing pediatric studies.

It is even more important for the new drugs coming down the pike because if we are going to invest early on, the needs of the pediatricians are early studies of those new drugs that are going to cure kids. We have got to get an incentive for those studies to be done early. That is why it works.

Mr. BUYER. Help me here. A drug manufacturer can only get the 6 month exclusivity if FDA gives it to you. What about can you ask for it? Can manufacturers ask for it?

Mr. SPIELBERG. We can propose studies, but one of the key issues in this whole issue in the accountability issue is that the FDA determines the precise nature of the written request. We can propose studies and then they can add on several additional studies, or change those studies. The FDA written request is the absolute sine qua non for us getting the exclusivity, but it also holds them accountable for the public health need and it holds us accountable for doing the right studies. That is why more than a third of the studies of those 411 are full efficacy studies. These are not simple PK.

Mr. BUYER. All right. Thank you.

In my questions, I refer to the pediatric exclusivity provisions of the report, January 2001 staff's report to Congress. I ask unanimous consent it be placed in the record. Hearing no objections, so ordered.

[The report is available at:]

http:///.fda.gov/cder/pediatric/reportcong01.pdf]

Mr. BUYER. I also refer to the Pediatric Studies Incentive: Equal Medicines for All, the white paper. This is what we're referring to as the Tufts report. I ask unanimous consent that it also be placed in the record.

Hearing no objection, so ordered.

[The report follows:]

THE PEDIATRIC STUDIES INCENTIVE: EQUAL MEDICINES FOR ALL

White Paper by Christopher-Paul Milne, Assistant Director, Tufts Center for the Study of Drug Development

INTRODUCTION

In November of 1997, the FDA Modernization Act (FDAMA) was signed into law, amending the Food, Drug and Cosmetic Act and the Public Health Service Act. The pediatric studies provision (Section 111) of FDAMA grants drug companies an additional 6month period of market exclusivity for new or marketed drugs in exchange for conducting pediatric studies requested by the FDA. FDAMA requires FDA to submit a report to Congress examining all issues relevant to the experience under the pediatric studies incentive program (hereinafter, the "incentive program"). In particular, the FDA is to focus on the effectiveness of the program in improving information, the adequacy of the incentive, the economic impacts on taxpayers and consumers, and suggestions for modifications. This white paper by the Tufts Center for the Study of Drug Development (Tufts CSDD) will provide an additional viewpoint on these and other relevant issues. This report is based on our own research as well as publicly available information, and focuses primarily on the present and future impact of the legislation as it relates to four areas of concern: effect on public health; building a pediatric research infrastructure; unforeseen impact; and, the cost-benefit ratio.

BACKGROUND

The 1962 amendments to the Food, Drug & Cosmetic Act made children *therapeutic orphans* because it required manufacturers either to test drugs in children or discourage their use in children with label disclaimer statements. Now, 40 years later, some 75% of marketed drugs are not labeled for use in children, despite the fact that many of them are therapeutically indicated for children and are used routinely off-label in the practice of pediatric medicine. This has resulted in a kind of ongoing *natural experiment.* Information on dosing, drug interaction, safety, and efficacy is developed, not in controlled trials that are carefully observed in a few hundred children, but instead in thousands of doctors' offices, homes, and hospitals, where hundreds of thousands of children may be exposed unnecessarily to adverse consequences before a drug is withdrawn or otherwise limited in its use.

The reason that these circumstances have persisted is that there are significant disincentives to studying drugs in children. These were noted in the Senate Committee testimony on the pediatric studies provision of FDAMA. They include a limited return on investment, liability concerns, and the difficulties of enrolling and studying pediatric patients (1). Although there were past efforts by FDA to encourage industry to study the pediatric uses of drugs developed for adults, these had been of a voluntary nature, either by design or default. The results were generally considered, even by FDA itself, to be "disappointing." In 1997, FDA proposed to make the study of pediatric indications mandatory. This crystallized a complementary effort by pediatric research advocates to get a pediatric studies incentive provision included in the FDA Modernization Act of 1997. The exodus of children from forty years in the desert of therapeutic exile was now to be driven by the carrot-and-the-stick.

EFFECTS ON PUBLIC HEALTH

The public health consequences of the existing situation are that, due to the lack of proper information, especially on correct dosing, and the lack of age-appropriate formulations, children are at an increased risk for under and overdosing, improper administration of the drug, and failure to follow the prescribed dosing regimen (i.e., noncompliance). In addition, children may be denied access to therapeutic advances because some practitioners might delay using a new drug on children off-label until there has been some experience with them in adults, or, they may never use what could be the best available treatment because it has not been properly formulated for children and may lack accurate pediatric use information. This problem of suboptimal utilization may be especially widespread in pediatric practice, because close to 40% of prescriptions for children are not written by pediatricians (2). Practitioners who are not routinely engaged in the care of children may be more wary of using medicines off-label in children.

Public Health Benefits of Improved Information

As a result of the incentive program, a great deal of information is being generated on pediatric indications for both new and already-marketed medicines. Of the 12 medicines labeled so far for pediatric use through the incentive program, one-third were medicines new to the market and two-thirds were already on the market (3). While just these few drugs have already made a significant contribution to improving therapeutic options and practice for hundreds of thousands of children (3), an additional 200 drugs could be labeled over the next few years. As of January 1, 2001, FDA reported that they had issued 39 written requests soliciting pediatric studies on their own initiative as well as 134 written requests in response to 210 proposed pediatric study requests (PPSRs) from industry (4).

There are indications that as many as three times the number of pediatric clinical trials may be ongoing now as were being performed in 1997, before the initiation of the incentive program under FDAMA (5). From September 2000 to January 2001, Tufts CSDD conducted a survey of drug companies that were the sponsors of the first 40 products receiving written requests.[1] Of the 25 survey responses, 16 enumerated the number of clinical studies conducted per request. There were 44 studies being conducted for 16 written requests. Assuming an average of close to three clinical studies per request, one can estimate that for the total number of written requests being undertaken under the incentive program, over 500 clinical trials in

[1] Sponsors for 25 of the 40 products responded to the survey (62.5% response rate). Of these 25 responses, 20 stated that pediatric study report submissions were planned or had already been sent to FDA. A review by Tufts CSDD indicated that 14 of these 20 products have, in fact, received pediatric exclusivity as of February 15, 2001.

children are currently being planned, conducted, or already completed, in comparison to less than 150 clinical trials in 1997 (6).

Dosing and use information, as well as the availability of appropriate formulations for pediatric indications of adult medicines will help make these medicines safer and more effective for children. At the same time, the upsurge in public attention and interest from the general medical community may also help alleviate the problem of suboptimal utilization in children of drugs developed for adults.

Public Health Benefits of Increased Pediatric Drug Research

The public health benefits that will accrue from increased pediatric research have already been recognized. In the few therapeutic areas in which there was considerable pediatric research already, such as AIDS and cancer, there has been a concomitant decrease in the adverse impacts of those diseases. For example, reported pediatric AIDS cases have declined 70% since 1992 due to the development of drug regimens to prevent perinatal transmission (7). Similarly, during the last few decades, well over 50% of pediatric cancer patients (the NIH reports it may be as high as 70% now) have been enrolled in clinical research, and today 75% of pediatric cancers are curable (8, 9).

Now under the incentive program, intensive research is being conducted not just in a few disease areas but on over 70 diseases and conditions of children (3). The majority of these diseases and conditions are in therapeutic areas in which scant research in children had occurred prior to the incentive program. However, these same therapeutic areas are the ones in which research is most urgently needed.

Tufts CSDD reviewed nine studies and reports published in professional journals or available from FDA, which discussed a variety of adverse outcomes in children resulting from interactions with therapeutic drugs. This review indicated that therapeutic areas historically involving high risk to children are prominently represented among the active moieties[2] (i.e., active ingredient) appearing on the original "FDAMA List" of active moieties for which additional information may produce potential health benefits in the pediatric population (10). An updated review by Tufts CSDD of those problematic therapeutic areas indicates that the top three (central nervous system, cardiovascular, and hormonal) correlate with the therapeutic areas covered by the three FDA reviewing divisions (neuropharmacological, cardio-renal, and metabolic & endocrine) receiving the most PPSRs as of January 2001—83 PPSRs or 40% of the total, for which FDA has already issued 59 written requests (4).

In addition to the number, breadth and public health significance of the diseases and conditions being addressed, dosing and use information is also being developed for the whole expanse of pediatric age groups. Of the responses to the Tufts CSDD drug company survey, 18 stated the age range for which pediatric studies were being done or had been completed. Tufts CSDD categorized the results using FDA age classifications.[3] The indication count by age-group was as follows: 4 for neonates; 8 for infants; 16 for children; and, 9 for adolescents. It is noteworthy that 32% of these studies included neonates and infants—age-groups for which little information was previously available.

More Child-Friendly Formulations Become Available

Besides age-appropriate use information, another key factor in making medicines safe and effective for pediatric patients is the availability of child-friendly formulations. Children are notoriously problematic when it comes to taking medications as prescribed by their healthcare practitioners. Children have documented non-compliance rates ranging from 50-75%, rates that worsen with chronic diseases such as asthma and diabetes (11). Disagreeable taste and difficulty in swallowing tablets or capsules, especially for children under six, are among the reasons for such high non-compliance in children (12). Besides decreasing the effectiveness of medicines, the lack of child-specific formulations increases the risks of adverse reactions for children, since they are exposed to doses and inert ingredients intended for use only in adults (13). Similarly, the use of extemporaneous formulations, which are pediatric preparations made by doctors and pharmacists from medicines only commercially available in adult product forms, increases the difficulty of accurate dosing and wastes staff time and money. One pediatric researcher noted that his children's hospital spent over 11 hours a day compounding extemporaneous products, and that

[2] Active moieties are defined by FDA as the molecule or ion responsible for the physiological or pharmacological action of the drug.

[3] Neonates—age 0 to 1 month; infants—age 1 month to 2 years; child—age 2 years to 12 years; and, adolescent—age 12 years to 16 years.

as many as 20% of medication errors in children may be attributable to such products (14).

The incentive program is improving this situation for children. The Tufts CSDD survey of drug companies shows that out of 20 active moieties for which pediatric studies were being done or already completed, 4 included the development of new pediatric formulations. Again, extending this experience to the rest of the 200 or so studies that are under way could mean that dozens of new child-friendly product forms could reach the market over the next few years.

Improving Global Public Health

As important as label information is for pediatric practitioners in the U.S., it is even more important to the practice of pediatric medicine in other countries. This is especially true in the developing world, where other forms of information, such as reference texts, may not be readily available and where care may have to be provided by individuals who are not professionally trained medical practitioners (e.g., government public health workers, humanitarian emergency personnel, missionaries, etc.). While the public health of children in the U.S. is the main focus of the incentive program, U.S. children will not be its only beneficiaries. A review by Tufts CSDD showed that approximately 70 active moieties that appeared on the 1998 FDAMA list also comprise nearly one-third of the World Health Organization (WHO) Essential Drugs List, a list of drugs determined to be critical to meeting the health needs of the world's nations (15). Despite the fact that many of the medicines on the Essential Drugs List are older, off-patent drugs used for treating acute conditions or tropical diseases, 18 active moieties of these drugs have been the subject of written requests already issued by the FDA. When these drugs are labeled for use in children and become available for distribution worldwide, the benefits of the U.S. incentive program will extend to all the world's children.

This, in turn, will help indirectly to further safeguard public health and safety here in the U.S. For example, AIDS has been declared a national security threat because of the destabilizing influence the epidemic is having on areas vital to U.S. interests. Along with AIDS, other diseases addressed by medicines eligible for the incentive program are transmissible and can cause transnational epidemics (e.g., tuberculosis, hepatitis C, and influenza). There are several million children residing in the U.S. that are recent immigrants for whom the public health toll can be ameliorated if labeled medicines for treating and preventing tropical diseases are available for use here as well as in their countries of origin (15, 16). Lastly, there is increasing recognition that the U.S. has a responsibility to help improve the public health of our international trading partners and geopolitical neighbors as part and parcel of the reality of globalization.

BUILDING A PEDIATRIC RESEARCH INFRASTRUCTURE

As Dr. Ralph Kauffman, a leading pediatric researcher and advocate, pointed out in a recent newspaper article: While an infrastructure for clinical testing of drugs for adults has evolved over the last few decades, that infrastructure never developed for children (17). There are very good indications that the infrastructure is now under construction as a result of the pediatric studies incentive program.

Effect on the Outsourcing Industry

Because of the rapidity with which the industry has had to respond to the pediatric studies incentive due to the deadlines inherent in the process of applying for the exclusivity, the major drug companies have had to marshal their resources very rapidly. The Tufts CSDD survey of drug companies shows that the initial sponsors responding to the incentive program accomplished this by diverting in-house resources and relying on outsourcing service providers. In fact, 8 out of 15 respondents to the question on the use of outsourcing said that outsourcing firms were employed to conduct all or part of the studies. The outsourcing industry consists of a number of service providers for a variety of clinical trial related tasks, ranging from data management to actually conducting clinical trials. Thus, the first building blocks of the nascent pediatric research infrastructure would appear to be found among the contract research organizations (CROs), site management organizations (SMOs), and independent clinical investigative sites that comprise the outsourcing industry.

A survey of 120 CROs by CenterWatch, an industry watchgroup focusing on the business of clinical trials, indicates that the number of CROs with pediatric trial expertise grew from 32% to 45% during 1997 to 1999 (18). At the same time, among 436 investigative sites, the number with pediatric expertise increased from 13% to 22% (18). Similarly, a group of non-profit academic SMOs, called the Pediatric Pharmacology Research Units (PPRUs), which is a network of academic medical centers specializing in pediatric research and organized under the aegis of the NIH, doubled

its number of participating institutions in 1999 from 7 to 13 in reaction to the increased workload from the pediatric research initiative (13). The PPRUs themselves may be working on as many as 70 industry-sponsored studies (19).

A Tufts CSDD survey of 35 CROs revealed that of the 21 respondents, 13 are working on pediatric studies.[4] These 13 CROs are collectively conducting 113 studies involving 7,000 patients. Just this sample of CROs and SMOs (representing roughly about 5% of their respective outsourcing service sectors) are working on nearly 200 pediatric studies themselves, compared to less than 150 pediatric studies involving drugs being done by the drug companies and outsourcing industry as a whole in 1997 (6). Half of the CRO respondents to the Tufts CSDD survey, who noted that pediatric research was responsible for most or some of the additional workload they had experienced in the last 2 years, said that this was due, in particular, to FDAMA's pediatric provision.

At the same time, the supply of researchers available to conduct pediatric drug trials appears to be increasing. There were fewer than 2,500 investigators with some degree of specialization or certification in pediatrics and current experience in pediatric drug research in 1997 (13). Soon after the incentive program was in full sway, stories in the media and trade press reported the creation of specialized pediatric research groups within two of the largest CROs—Quintiles and Parexel. In addition, two large SMOs have launched pediatric-specific ventures—Pediatric Clinical Trials International and Kelson Pediatric Partners, which collectively can call on the services of 500 doctors with pediatric training and nearly 2,000 investigators. This increase in personnel dedicated to conducting pediatric clinical trials was also evident from our survey of CROs. Of the 13 CROs currently conducting pediatric studies, 4 had added staff explicitly for pediatric studies—on average about 3 staffpersons per CRO. Also, 3 of those 4 CROs had created new units within their organizations dedicated specifically to pediatric drug clinical trials.

FDA Acknowledges Increase in Pediatric Studies of Drugs

FDA recognizes the extraordinary growth that has occurred in the field. When CDER announced the creation of a new position—science director for pediatrics—it stated that the responsibility of the new position was to focus on the rapidly expanding field of pediatric clinical trials (20). In a recent quote from USA Today, FDA's Associate Director for Pediatrics, Diane Murphy, predicted that the number of unlabeled medicines on the market for children will decrease from 75% to 50% over the next 5 years (21). According to an unpublished Tufts CSDD review of efficacy supplements approved from 1995-2000, this change may already be taking place. Before FDAMA, from 1995 to 1997, there were only 39 efficacy supplement approvals on the basis of new research for pediatric indications. Since FDAMA, from 1998 to 2000, that number has nearly doubled to 71.

Science of Conducting Pediatric Trials Has Been Advanced

The science of doing research in children is also evolving as the architects of trial protocols must design new approaches for studying pediatric patients in clinical trials. The Tufts CSDD survey of drug companies indicates that population pharmacokinetic studies have been done for 13 of 20 active moieties. Population pharmacokinetic studies are a nontraditional approach to studying the effects of the drug on the body that requires fewer invasive procedures to be performed on each patient. For 2 active moieties, long-term follow-up studies were being conducted. This is a time-consuming type of clinical investigation recommended by FDA for chronic-use and preventative drugs, but which in the past has been done infrequently. In addition, sponsors developed 3 new biological sampling techniques and 4 new clinical or surrogate endpoints (i.e., measures of benefits derived from the treatment). An example of one newly created measure of clinical benefit was the development by one sponsor of a novel rating scale for anxiety in pediatric patients. The lack of measures for clinical benefit from therapeutic agents for pediatric anxiety disorders had previously hampered proof of efficacy for such drugs. If the advances resulting from just these few pediatric studies are representative of the several hundred studies now under way, the science of pediatric clinical trials has come a long way in one-tenth the time it took to develop the research infrastructure for adult medicines.

[4] In the fall of 1999 and winter of 2000, Tufts CSDD conducted a follow-up survey of 35 CROs who had responded to an earlier survey distributed to all CROs with exhibition booths at the 1998 Annual Drug Information Association meeting. The response rate was 60% (21/35).

UNFORESEEN IMPACT

Although there were some predictable outcomes from the pediatric studies incentive program such as the vigorous response by the drug companies, a host of unforeseen effects have occurred as well—by-and-large these have all been beneficial.

Other Countries Emulate U.S. Incentive Program

Due to the example of the U.S. program, which has been applauded in the United Kingdom, Canada, and Europe, there has been a dramatic upsurge in international activity related to pediatric research. Numerous studies and reports have been published over the last several years documenting the use of off-label drugs for children in various countries throughout the world, such as Australia, Japan, Britain, Canada, and the Netherlands. Two international groups that provide recommendations on the evaluation of therapeutic drugs, the European Medicines Evaluation Agency (EMEA) and the International Conference on Harmonization (ICH), have published guidelines on the conduct of clinical trials in children, and noted the need for more pediatric research as well. The European Union's Council of Health Ministers recently adopted a resolution that also recognized this need and invited the European Commission to make appropriate proposals for incentives, regulatory mandates, and other supporting actions to address this urgent problem (22).

Pediatric Provision Complements FDA Modernization Act and Orphan Drug Act

The pediatric provision has had a synergistic effect with regard to other provisions of FDAMA and the Orphan Drug Act (an R&D incentive program for medicines addressing rare disorders). A survey by Tufts CSDD of companies engaged in the development of fast track products for serious and life-threatening illnesses (FDAMA Section 112) demonstrated that close to half of them (11/23) were being studied for pediatric indications as well as for adult indications (23). Similarly, a Tufts CSDD survey of biotechnology and pharmaceutical companies on the use of the single controlled trial for proof of efficacy (FDAMA Section 115) showed that half of the respondents were doing so for pediatric or orphan indications (24).

Orphan drugs often include indications for pediatric use because many rare diseases are genetic or metabolic in origin. In fact, the FDA's Office of Orphan Drugs has provided support for some early development work on pediatric indications of drugs by non-industry sponsors. These sponsors then interest the drug companies in pursuing these indications for pediatric exclusivity, as occurred recently with the drug propofol (25).

Pediatric Research Benefits Adult R&D

Another unanticipated outcome from the incentive program is that researchers are now looking both ways—up and down the age scale. Not only are drugs for adults now being developed with a view towards their pediatric uses, but the reverse is happening as well; drugs and drug formulations developed for children are being extended to adults. For example, TPIO is an investigational drug being studied as a potential treatment to improve post-operative outcomes in infants undergoing cardiac bypass surgery. The sponsoring company has been buoyed by its success with trial results in the targeted population of infants and has decided to extend its investigation to adults (26). Similarly, results of studies to support the pediatric exclusivity application for the AIDS drug abacavir were later extrapolated to adults to support approval of the drug for that population (27).

Pediatric formulations of drugs designed to ease administration of medicines in children, and thus increase compliance, can be utilized in other difficult-to-treat populations, such as the elderly or adults who have difficulty swallowing pills. For example, Ascent Pediatrics' Primsol was developed for children as the first liquid formulation with trimethoprim (an antibiotic) as the sole active ingredient, for the treatment of otitis media in children. However, in addition it has recently received approval for a second indication—the treatment of urinary infection in adults (28).

Development of Rigorous Ethical Standards for Pediatric Research Gets Increased Attention

The pediatric studies incentive has focused media, government, and industry attention on pediatric research. The Boston Globe recently published an article detailing a number of pediatric clinical trials investigating drugs and other therapies in which there were ethical issues and safety concerns (5). Although few of these trials were conducted for the purpose of pursuing pediatric exclusivity, and the trials were conducted at various research facilities including state and federal government institutions as well as academic medical centers, the incentive program was the impetus for bringing them to public attention.

There is now a growing awareness that pediatric clinical trials require special considerations in their design, additional safeguards in their implementation, as well as specially equipped facilities and appropriately trained personnel. There is a consensus now among international bodies, which provide guidance on clinical research (e.g., the EMEA and the ICH), that it is necessary to address the ethical issues inherent in pediatric research, along with the scientific, technical, and practical ones. In the U.S., the incentive program has been the impetus for FDA's convening a Pediatric Ethics Working Group within its Pediatric Advisory Subcommittee to assist FDA in addressing ethical issues in pediatric research. The NIH instituted a policy coincident with the advent of the pediatric studies program stating that children must be included in all human subjects research funded by the NIH unless there are scientific or ethical reasons to exclude them. The NIH policy also requires research plans to detail the capacity of the researchers to provide appropriate pediatric expertise and facilities (29). The 106th Congress, as well, just recently enacted the Children's Research Protection Act to increase safeguards for children involved in research and to provide funding for the study of pediatric pharmacology (30).

Public Health Risks of Off-Label Use Viewed as Outweighing Risks of Research

Without the impetus of the pediatric studies incentive program, it is possible that pediatric clinical trials would have remained in the backwater of the research mainstream and ethical problems may have continued to come in under the radar screen of public scrutiny. Moreover, 40 years worth of natural experiments—using drugs in children that had been studied only in adults—would have been ignored. There is an uneasy balance that must be negotiated when weighing the risks from increasing research on children and using drugs off-label. This tension was highlighted recently by a prominent pediatric practitioner and professor of child health from the United Kingdom, Professor Choonara, who was applauding the American pediatric studies initiative in an article published in the British Medical Journal (31). Choonara pointed out that the alternative to not doing pediatric trials is the continuance of using medicines in children without any evidence base. Such a situation, Choonara believes, recently lead to the deaths of 15 children from the use of a sedative in critically ill children. Choonara asserts that if this medicine had been studied as part of a clinical trial, one death would have led to an urgent reappraisal of the trial and the treatment (31). That child's death would have been a tragedy, but one that might have prevented 15 other tragedies.

COST-BENEFIT RATIO

As noted previously, children have been effectively denied access to safe and effective medicines, since 75% of marketed drugs are not labeled for pediatric use. This leads to underutilization of what may be, not only the best treatments available, but the most cost-effective ones as well. Studies by managed care organizations have found that treatment with medicines may often provide the most cost-effective therapeutic option (i.e., as opposed to surgery, lifestyle management, no treatment, etc.) and that they can also lower complications from disease as well as decrease rehospitalization rates (32). As importantly, healthy children become healthy adults; much adult illness and distress has its origin in childhood (33). Any investment that we make in the short-term now to improve children's health could result in tremendous health care cost savings in the long-term. The economic value of reducing mortality from just cardiovascular disease alone is a staggering $1.5 trillion annually (34). An estimated 13% reduction in mortality from such cardiovascular-related events as heart attacks and strokes is attributable to new drug therapies that reduce blood pressure and cholesterol (34).

Economic Impacts of Leading Causes of Death in Childhood from Disease

Among the leading causes of death for children in 1997 are a number of illnesses that can be mitigated, cured, or prevented by drug and biological products currently on the market or in development, and whose annual economic impacts for 1998 have been quantified (see Table 1).

Table 1. Annual Economic Impact and Rank as Leading Cause of Death (1997) for Diseases Treatable with Pharmaceuticals in U.S.[5]

Rank of Disease Among Top 10 Causes of Death by Age Group

Disease	Infants (>1)	Children (1-14)	Youth (15-24)	Adult (25+)	Economic Impact (per year, in billions)
Heart Disease	5	5	5	1	$286.5
Pneumonia/Resp. Infection	6	7	8	4	$12.0
Stroke (Cerebrovascular)	8	10	9	3	$45.3
Infectious & Parasitic Disease	9	.....	.....	.....	$12.0
Cancer	.....	2	4	2	$149.1
HIV	.....	8	7	.....	$64.1
Bronchitis/Asthma/Emphysema	.....	9	10	5	$46.5
Diabetes	.....	.....	.....	6	$98.0
Total	4 of top 10	6 of top 10	6 of top 10	6 of top 10	$713.5

Adapted from ''Kids at Risk,'' Harvard Center for Risk Analysis, April 2000; and, ''Top Ten Disease Categories by Cost,'' Pharmaceutical Research and Manufacturers of America, December 1999 (35, 36).

[5] Other conditions or events not listed in Table 1 which are among the ten leading causes of death for the various pediatric age-groups shown are: certain conditions originating in the perinatal period; birth defects; ill-defined conditions; unintentional injuries; homicide; certain intestinal infections; and, suicide (35).

If even one-hundredth of the annual economic impact from these leading causes of death and disability (see Table 1) was reduced by providing more effective treatments to children, making for healthier adults in the process, the $7 billion saved each year would be 10 times more than the nearly $700 million that FDA has estimated as the yearly cost to society from the pediatric exclusivity awards (3). Currently, $45 billion a year, just 56 cents per person/per day, is spent on medical and health research by all sources of funding (34). The $700 million annual costs of the incentive program would add an extra penny per person/per day, and be well worth the bargain.

Treatment for Childhood Mental Illness Needs More Therapeutic Options

Even analyses of diseases that are leading causes of death do not begin to tell the story of potential healthcare cost savings from the pediatric studies program. One in ten children in the U.S. suffer from mental illness severe enough to cause impairment, yet fewer than 1 in 5 receive treatment (37). Again, these childhood disorders make for unhealthy adulthood; 74% of 21-year-olds with mental disorders have a history of prior problems (38). Yet, there are few psychotropic drugs approved specifically for the treatment of pediatric psychiatric disorders (38). The economic consequences of mental illness are staggering—$42 billion a year just from anxiety-related disorders such as panic attacks and obsessive-compulsive disorder, with 40% of the population affected being children (39), and an additional $44 billion for serious depression (40). For the nearly 4 million children affected with ADD/ADHD (41), median per capita annual health costs are more than double that of an unaffected child (42). No wonder that for the year 2000, the legislative agendas of 19 states included bills related to children's behavioral health (43).

The incentive program is helping to address the need for more therapeutic options to treat mental illness in children. The therapeutic area for which drug companies have submitted the greatest number of study proposals (29 PPSRs as of January 1, 2001) under the incentive program is neuropharmacological drugs. Pediatric studies have already been completed for 4 of these drugs, and 3 have been labeled for pediatric use.

Health and Economic Needs Addressed by the Incentive Proizram Are Unappreciated

A concern expressed by some critics of the incentive program is that awards have been granted for medicines treating diseases and conditions with little impact on the pediatric population, but which are very lucrative for the sponsors of the drug (44). One such condition is high blood cholesterol levels, considered a risk factor for heart diseases and stroke. It is worth noting that 36.5% of children in the U.S. have high cholesterol levels, according to one report (45). Arthritis and hypertension are other illnesses that some assert are not pediatric problems, yet the prevalence of rheumatoid arthritis in U.S. children is between 71,000 (46) and just under a 100,000 (17), while that of hypertension is estimated to be 1% of the pediatric population, or some 750,000 children (47).

Other conditions are criticized as being of minor clinical significance for children, but of major importance for drug company profits (44). One such condition is seasonal allergic rhinitis (SAR). Yet at a time when the academic performance of Amer-

ica's children is of paramount concern, the impact of this condition is anything but minor. SAR affects 10% of school-age children, causing missed school days, poor school performance, and impaired function on standardized tests (48).

An unappreciated healthcare cost efficiency potentially realized through the auspices of the incentive program is Medicaid cost savings. As of 1995, some 17 million children were covered by Medicaid (49). An additional 7 million of the nation's 11 million uninsured children are now eligible for coverage under state Child Health Insurance Programs (CHIPS) or Medicaid expansions (50), so that potentially 25 million children will be covered by federal and state programs within a few years. In fact, a spokesperson for one children's hospital in Florida noted that 60% of their pediatric patients are Medicaid-dependent (14).

The potential healthcare cost savings that could be realized through improvements for therapeutic options in children are difficult to overstate. For example, the annual costs for treating Medicaid-dependent children for just three diseases listed in Table I—AIDS, asthma, and diabetes—could be nearly double (~$1.2 billion) FDA's estimate of the yearly costs to society from the incentive program (36, 51-56).[6]

Costs to the Poor and Elderly Are Not Unreasonable

One concern about the cost-benefit ratio of the pediatric exclusivity program that has been voiced is the impact of the additional period of market protection on the prices of drugs for the poor and elderly. Ironically, sacrificing the affordability of medicines to the poor for the sake of availability to children is not really an issue. Children are the poor! Close to half of the Medicaid population (42%) are children (57). Another large percent of the poor are the families of those children. Denying children access to labeled drugs, denies poor children access to the best available treatment. It also makes poor parents pay more out-of-pocket. Medicaid usually provides a drug benefit, but often it may not cover off-label drugs, except for cancer and AIDS medicine (13).

The real question then, is what is the trade-off as far as the elderly are concerned. At first glance, this appears to be a genuine point of contention, especially as Congress contemplates extending Medicare benefits to include prescription drugs. A comparison of the top 50 drugs used by the elderly (58) with the February 2001 list of drugs issued written requests, reveals that 4 of the top 10 and 22 of the top 50 drugs for elder care are the subject of written requests, and thus potentially extended market protection. This theoretically could delay access to less expensive generic versions of certain commonly used drugs in elder care. However, a closer look at the list reveals that there would be somewhat of a lesser impact than it would first appear. Four of the 22 drugs are different strengths of the same drugs, reducing the number on the list to 18. An additional 7 are therapeutically similar to other drugs on the list and are in therapeutic categories for which there are a number of available alternatives on the market besides the ones on the list (i.e., GERD, antihypertensives, and lipid-lowering drugs). This reduces the number of drugs commonly used by seniors that could be impacted by the incentive program to 11. For those 11 drugs, it is unlikely that any senior would be using more than two of these drugs at exactly the same six-month period that they may be protected from generic competition. In addition, many of the elderly, if they are poor or low-to-middle income, have some form of prescription coverage through Medicaid and state drug assistance programs for seniors (59). So, while a statistical analysis could generate high dollar numbers indicating an impressive detriment to the public coffers in theory, the actual out-of-pocket expense for any senior citizen is likely to be minimal and temporary.

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[6] For AIDS, Medicaid paid out an estimated $3.9 billion in 2000. The percentage of all AIDS victims that are children and teenagers is about 5-6%, but Medicaid pays for about 90% of those costs as opposed to 50% of adult costs. So, the toll for pediatric AIDS comes to about $190 million (36, 51, 52). For asthma, the cost to Medicaid and Medicare exceeds $1 billion. Given the high mortality rate of asthma in the elderly, the eligibility of poor or disabled, elderly asthmatics for Medicaid, limited drug benefits in Medicare, and the fact that only 13% of the population are elderly, it is likely that only about 10% of these costs are Medicare. Of the remaining $900 million, pediatric asthmatics could account for as much as one-third of those costs (~$300 million) since they comprise one-third of the asthmatic population overall and have higher hospitalization rates (53, 54). For diabetes, the CDC estimates that 5-10% of diabetes is type 1, typically diagnosed in childhood. The American Diabetes Association reports that diabetes cost Medicaid $10 billion in 1997. A conservative estimate (since it does not take into account the small but growing population of pediatric type 11 diabetics) of pediatric costs for diabetes would be $750 million (55, 56). Adding these costs together amounts to ~$1.2 billion annually.

Costs to Taxpayers and Consumers Are a Matter of Social Equity

As for the putative cost to taxpayers and consumers in general, again at first glance, this could seem like an unfair bargain. Data for 1999 show that 5 of the top 10 and 22 of the top 50 prescription drugs by sales (60) have active moieties, which are the subject of written requests, again indicating potential increased costs due to delayed availability of lowerpriced generic alternatives. However, another way of ranking the top prescription drugs reveals that there is a social equity factor to be calculated in the cost-benefit equation. Eight of the top 10 and 28 of the top 50 prescription drugs by number of prescriptions written (61) also contain active moieties for which FDA has issued written requests soliciting needed pediatric studies. Thus, many of the most commonly prescribed medicines currently available for the general population are not adequately labeled for use in children.

Yet, making these commonly used drugs available to children is not likely to significantly increase costs for the government or other third-party payers. Children are something of a bargain when it comes to prescription drug costs. The average toll for a month's worth of prescription medicines for children and college students is only $10; adult prescription needs are 3 times more expensive and seniors are over 10 times as costly (62).

Concern that increased availability of medicines for children will lead to overuse is probably not warranted either. In fact, there is some evidence to suggest that pediatric practitioners are becoming more judicious in their use of medicines in an area formerly thought to be rife with overuse. The National Center for Health Statistics has determined that the number of antibiotic prescriptions written per 1,000 children declined by 34% from 1990 to 1998 (63).

The social equity factor becomes increasingly weighty when one considers that society in general has historically overlooked the health needs of children. A 1997 survey found that only 4% of the public felt strongly enough about issues of children's health to have written or spoken to public officials about them within the last year, whereas 4 times as many had contacted public officials about Medicare and Social Security issues (64). Yet, children are less likely to have a regular source of medical care. For example, among the elderly, only 4.1% did not have regular access to medical care (65), while among children, 6.5% do not have regular medical care (66). An estimated 13% of U.S. children also lack health insurance, leaving them 3.5 times as likely to go without needed medications and mental health care compared to insured children (66). Although children comprise 27% of the general population in the U.S., they comprise 42% of the poor in this country (57), circumstances which, by themselves, contribute to poor health outcomes for children later in life, such as stroke and certain cancers (67). The incentive program represents one of a series of steps necessary to address the fact that children have been overlooked by the present-day healthcare system.

Liability Costs Affect Everyone

A review by Tufts CSDD of tort litigation cases from the late 1960s to the mid1990s, which were compiled in a 1998 legal compendium (68), indicates that of 147 active moieties listed by FDA as having received written requests by February 15, 2001 (4), 19 had been the subject of litigation. One active moiety, which as of 1997 was the subject of some 270 cases, was excluded from the review because settlement or award amounts of the few cases resolved in favor of the plaintiffs were not known. The other 18 active moieties were the subject of 76 cases: 60 alleging injury to adults and 16 injury to children. Of these 76 cases, settlement or award amounts were reported for 22. The total amount awarded to plaintiffs was over $82 million exclusive of court costs, legal fees, expert witness fees, and other charges. The average amount awarded in adult cases was $671,813, while in cases involving children the average award was $898,100 (excluding one case with a 20-year-old college student as the plaintiff that resulted in a $67 million award). Because of the lag time involved in cases reaching the courts,[7] it is likely that few drugs approved in the 1990s are represented here, and some of the cases are 20-30 years old, when awards were generally for lower amounts. For example, some of the award amounts sought by plaintiffs in more recent cases that are still pending before the courts were in the neighborhood of $100 to $155 million. Moreover, 90% of actions never reach court, some state cases are unreported, and settlement amounts are often undisclosed as part of the settlement agreement. Thus, the actual litigation costs from cases involving these active moieties could be many fold higher.

[7] Typical malpractice awards in 1996 were from incidents that occurred in 1988 (69), and a similar lag effect is likely in product liability cases as well.

Table II. Average Payouts by Type of Defendant from 22* Litigation Cases Involving Drugs Receiving Written Requests (*3 cases had multiple defendants; for 2 of these, total liability amounts were attributed to both defendants)

Average Award or Settlement Amount	Type of Defendant, Number in Parentheses ()
$33,632,500	Manufacturers (2)
$1,324,000	Hospitals (5)
$784,500	Medical Doctors, Dentists (15)
$1,020,000	Government (2)
$67,000	Medical School (1)

As seen in Table II, the defendants were not manufacturers by-and-large, but doctors and hospitals. So, while manufacturers are justifiably leery of litigation because of the size of the awards against them, liability fears affect all levels of health care, from medical students to liability insurers. It is also worth noting that prospective litigation costs may be passed along to consumers and taxpayers in the form of higher drug prices. A study published in 1997 found that liability risk is responsible for one-third to one-half of the price differential between the United States and Canada where drugs are substantially lowerpriced (70). Thus, any liability avoided by better labeling for drugs used in children, especially since they typically involved more costly awards in this sample of cases, will be beneficial across all segments of society.

Costs to Industry

The FDA report to Congress detailed the "costs" to the generic and retail pharmacy industry (3). However, these are not really costs but "unrealized profits" from the lengthening of the period of market protection for some brand-name drug products. Yet, generic manufacturers are not forced to enter the market for any particular drug product, and they are already selective as to where they choose to compete. For example, there already exists a portion of the pharmaceutical market comprised of drugs unprotected by patents and without generic competition that is nearly equal in dollar volume to the current portion of the market held by generics (71). So, the incentive program is not actually costing the generic industry anything in terms of losses of current market share or actual expenditures for increased staff, equipment and facilities, but from a delay of future profits. Since the "costs" to the retail industry are based on the higher mark-ups they can command for generic drugs over brand-name drugs, their costs also are not actual losses or expenditures, but unrealized profits.

In contrast, the costs to the brand-name drug companies can be stated in terms of time, staff, and actual dollars spent. The Tufts CSDD survey of drug companies indicates that the costs of the trials have not been particularly high, averaging $3.87 million per written request, although ranging as high as $20 million. The per-patient costs have been somewhat higher than expected, averaging $20,405 per patient compared to FDA's estimate range of $5,000 to $9,000 (72). The average number of patients, based on 15 responses to the Tufts CSDD survey, was 203 patients per written request. If these figures are representative of all pediatric studies that are under way for the 173 written requests issued as of January 1, 2001, then drug sponsors will spend approximately $717 million on pediatric studies under the program. Taking into account the reported average costs from our survey for formulation development of $750,000 per formulation and that one-fifth of the written requests in our survey required a formulation to be developed, that amounts to an additional $26 million. The total then would be close to $750 million.

However, clinical investigations of as many as 250 active moieties (i.e., from 210 industry PPSRs and 39 FDA-initiated written requests) may be in process already. Considerable expenditure will accrue to any sponsor conducting pediatric clinical trials even if the studies are not ultimately completed. In the Tufts CSDD survey of drug companies, only I out of 25 respondents did not submit a PPSR and had no plans to submit pediatric study reports. This suggests that only 4% of sponsors will not undertake at least some work on any active moiety that is the subject of either an industry study proposal or FDA-initiated written request. It would not be unreasonable then, to estimate that industry costs could climb upwards of a $1 billion for the 250 active moieties being studied under the current incentive program. This may be a conservative figure, as a year still remained in the statutory period when this estimate was calculated.

In actuality, the drug companies never really balked at the actual cost in dollars for doing the studies (13), but more so the limited return on investment, and hence

the opportunity costs of investing resources needed elsewhere. The studies do take time, on average almost 2 years (22.75 months) according to the Tufts CSDD drug company survey, and some companies have been at it for as long as 48 months without nearing completion. Also, the studies take considerable numbers of personnel. From the number and types of studies reported in the Tufts CSDD survey and published numbers of staff typically utilized for each type of study (13), we estimated that each written request required 21 full-time staff-persons. For 173 written requests that would entail the services of close to 4,000 research personnel (and over 5,000 staff for the 250 active moieties that are likely to be studied).

The reason that opportunity costs and hence dedication of resources are so critical is that pharmaceutical companies compete not only among themselves, but also with other industries for investment dollars. In order to maintain a growth rate of 10% and continue to attract investors, pharmaceutical firms must produce 3-5 new chemical entities (NCEs) per year, with sales potential of over $350 million per year—so-called blockbuster drugs (73). These competitive pressures have reputedly been one impetus for all the merger activity that has taken place over the last few years. The response by the firms to the pediatric studies incentive has been robust, but only because it was attractive enough to lure some of their attention away from other mainstream R&D activities. The pediatric sales market itself is insufficient to render the commitment of resources profitable. In fact, when the European Union's Council of Health Ministers recently discussed possible approaches to encouraging more pediatric research, it noted that R&D costs are not amortized because of the small number of children affected by each disorder in an age bracket (22).

Reauthorization of the Incentive Program with Modifications Is Necessary to Ensure that Benefits Accrue to All

As costs of the incentive program do not accrue equally across all economic sectors neither have the benefits been spread equally among all putative beneficiaries. Neonates, in particular, have been a problematic age-group within an already problematic sub-population. While the lack of information is an especially critical concern in this age-group, the barriers to conducting such studies are especially onerous, not the least of which are the difficult risk-benefit decisions facing the IRBs that must approve such studies. However, more headway has been made with neonatal studies through the incentive program than with regulatory approaches.[8] But much remains to be done. The 1998 FDAMA list noted that approximately two-thirds of the active moieties listed needed information for the neonatal age-group, but the Tufts CSDD survey indicates that only one-quarter of active moieties are currently being studied for use in neonates under the incentive program.

Similarly, active moieties for cancer drugs appear to be a disincentivized therapeutic area. Although 12 written requests had been issued as of January 1, 2000 by FDA's Review Division for oncology drugs, 9 of those were issued just since October 1, 2000, and no pediatric exclusivities have been granted yet. Also, for most active therapeutic areas under the incentive program, there are more PPSRs than written requests. For oncology drugs there were only 8 industry proposals. This could reflect reputed difficulties in this therapeutic area such as demanding clinical trial requirements and scant availability of patients. In fact, it is likely to remain problematic to sufficiently incentivize the study of older oncology drugs. Efforts may be more fruitfully devoted to establishing special incentives for oncology drugs in development so that children have access to therapeutic advances as soon as possible, if there are no better treatment options available.

As for other therapeutic categories that have not resulted in any pediatric exclusivity awards (i.e., medical imaging, reproductive, and anti-infective drugs), medical imaging products are used for diagnostic purposes and study participants may be difficult to recruit, especially as a protocol involving the use of healthy children or patients with an illness unbenefited by medical imaging may not pass the risk-benefit threshold of IRB review. Reproductive drug needs are limited for this age-group. Anti-infectives are problematic because antibiotics approved before the passage of FDAMA are not eligible for the incentive. While a number of antibiotics are labeled for children, some needed ones are not. Again the solution may be to incentivize the development of pediatric indications for new antibiotics so that they can replace older marketed ones that are unlikely to be studied under the incentive program in any case.

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[8] For example, 11% of studies done in response to written requests included neonates according to the Tufts CSDD survey of drug companies, while only 5% of pediatric studies done to comply with the 1998 pediatric rule were for neonates according to Tufts CSDD annual surveys of marketing applications for NCEs from 1997-1999.

Congressional intent was not to limit the benefits of improved information on the pediatric uses of drugs to some children, but rather to extend them to all children. The following recommendations for modifications to the incentive program should help to address this goal:

- Pediatric Studies Provision—first and foremost, the pediatric incentive program under FDAMA should be extended for another five years for all eligible active moieties in order for the pediatric research infrastructure to become selfsustaining and for the other benefits discussed in this white paper to be realized for the long-term.
- Pediatric User Fees—the report by FDA to Congress (3) and the fact that over 65 FDA personnel are currently listed as participating in 12 pediatric oversight activities (12) demonstrate that FDA needs dedicated resources for the incentive program to fulfill its goals. These should be generated by pediatric exclusivity application fees.
- Treatment INDs—drugs in development which are made available to children with serious or life-threatening illness, such as cancer, under an expanded access protocol for a sponsor-submitted treatment investigational new drug application should be granted a 6-month transferable exclusivity award upon acceptance of the pediatric study reports for the active moiety by FDA.
- Neonatal Studies—sponsors that develop neonatal indications for already-marketed drugs should be granted a 6-month transferable pediatric exclusivity period.
- Unmet Medical Needs—sponsors that develop pediatric indications for already-marketed drugs that address serious or life-threatening illnesses or diseases/conditions for which insufficient treatment, prevention, or diagnostic options currently exist should be granted a 6-month transferable pediatric exclusivity period.
- Antibiotics—sponsors that develop pediatric indications different from the adult indications for new antibiotic drug applications should be granted a 3-month transferable pediatric exclusivity period.

CONCLUSIONS

The pediatric studies incentive program was added to FDAMA in recognition of the special needs and concerns attendant with developing medicines in children. It took 40 years for the research based pharmaceutical industry to build the current R&D infrastructure. It was built for adults. Accommodating it to provide for the needs of children will take more than 4 years. It will require significant investment of time, money and personnel. Some business sectors will gain, while others will not. Yet, the ones gaining are also the ones taking the risks and doing the work. In the short-term it will require some trade-offs, by Americans as taxpayers and consumers for the sake of Americans as children, parents, and grandparents. In the long-term, we all stand to share in the benefits of equal medicines for all.

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Mr. BUYER. I now yield 5 minutes to Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. Franson, the FDA briefed this committee that the highest end of what a single ped trial costs is $4 million. Do you agree with that figure?

Mr. FRANSON. I would not agree that a large scale clinical trial involving hundreds of thousands of patients would be that economical.

Mr. STUPAK. So you are saying it would be more?

Mr. FRANSON. I'm saying that depending on the number of patients and the complexity of it, the cost would be proportionate. I am not sure what assumptions were factored into the FDA estimate.

Mr. STUPAK. What would a $4 million study get us? Can you give us the size and the type of complexity we are dealing with here?

Mr. FRANSON. Well there's a lot of factors one would have to sort out. In other words, is it a long-term or a short-term therapy. Does it require single or multiple comparisons to established drugs? Based on all of that, one would have to then frame how much.

Mr. SPIELBERG. To give you some additional insight, even a simple pharmacokinetic study which will be done on adults at a single center with 20 normal volunteers, when we do one of those pharmacokinetic studies, we usually do it at half a dozen, maybe even 10 centers, such as the pediatric pharmacology research units. That means two or three patients per center. That means vastly increased internal costs as well because we have to send out monitors to each of those sites. We have to provide drugs to each of those sites. Vastly more complicated.

The pediatric efficacy studies that we do are again, much more complicated. We agree completely that the ethics and the way in which these studies are done are critically important. So we have to monitor more closely. We have much more complexity in doing the studies. So that if you look at your average adult study and

your average pediatric study for a comparable number of patients, in fact the costs are greater for the pediatrics.

Mr. STUPAK. Dr. Franson, in some testimony back and forth there, I just want to make this point. No one is suggesting that the PDUFA and its user fees increase withdrawals or recalls of drugs. But I think what people are asking is whether the tight timeframes that's under FDAMA have increased withdrawals by rushing review. That is our concern, is is the tight timeframe rushing review. I noticed in your testimony you indicated there's been six drugs recalled in 5 years, but everything we have seen and heard today, it's really 11 drugs in about 4 years. So there is quite a disagreement there.

I made the analogy earlier of an airplane accident, so you have 10 airlines, you have one accident, and now you get to 100 airlines with 10 accidents. To a lot of us, that's not acceptable. Our concern is are we rushing things here with this review?

Mr. FRANSON. I appreciate that question. My response to the pre-PDUFA drugs was of that complement of 11, four of those were in the pre-PDUFA era. So there would have been no possibility for a compression of review.

I would also look at the quality of review during the time of PDUFA and say in general, exceptionally high. Also, that none of these reviews to my knowledge have eventuated in an abbreviated review of safety.

I would almost look at the PDUFA phase and say it actually is evidence that new attention to direct review is actually helping the overall surveillance process. I would also point to the fact that in the last 3 to 4 years, FDA has constituted a new Office of Postmarketing Drug Risk Assessment, that they have the new Med Watch programs, and in essence, they have capacity and also systems to do a better job.

Mr. STUPAK. But even on the Med Watch program, that's really directed only to the health care professionals. It is not given to the general public. If you are relying on the public to tell you an adverse event reaction on a drug by only giving notice under Med Watch to the physicians, how is the general public going to help you monitor these drugs and do the volunteer reporting that you rely upon for the accuracy of the drug and make sure you're not having an adverse effect, when Med Watch is only within.

I have read and seen enough articles that say once a drug is labelled and out there, doctors don't go back and review the labelling. They just don't do that. They rely upon the initial labeling of that drug, and that's what they use it for, unless someone, with all due respect, hits him or her with a hammer, then he'll start to realize that hey, there's been some changes. Med Watches don't work. That Med Watch and "dear doctor" letter goes to the doctors, not to the consuming public.

One more, they have asked me to ask you. What do you believe is the mean, median, and mode of the trials done for pediatric exclusivity, cost? They forgot cost in there. For cost. If you want to just submit that later.

Mr. FRANSON. We would be happy to assess that and provide written comment. We would ask that we do that with some assumptions included so that we're accurate.

Mr. STUPAK. Let me follow up with one more, if I may. We were talking about Med Watches and all that. In the PDUFA and all that, we tried to do mandatory post-marketing survey while having the drug companies pay for it. That has always been resisted by the drug companies. Why is that? I mean if you pay to have an expedited review to get the drug on the market quicker, then why wouldn't the drug companies, pharmaceutical companies, be willing then to pay for post-marketing review? That's when we really see how a drug works in the real world, not under the Phase I, II, or III, which are really sort of set clinical trials. So why wouldn't the pharmaceutical companies be receptive to it?

Mr. FRANSON. I'm not sure I could respond for every company. I would say in certain drugs at the present time there are actually Phase IV agreements for monitoring, for patient registries. I think that depends on the particular compound. So there are at least, I'm sorry I can't quote you the number, but we would be happy to provide that, where agreements have been reached.

Most companies provide study follow-up in certain settings, be they large HMOs which have data bases for follow-up. I am sure that given the stipulations of those kinds of studies, we would be happy to investigate and assess further.

Mr. STUPAK. Well, when you take a look at it, in 1992, when the first PDUFA came out, we couldn't get it in there. In 1997, it was actually written in the law that we wouldn't be charging, pharmaceutical companies would not have to be charged for post-marketing surveys. That really was at the request of the pharmaceutical companies.

I am just trying to figure out why is the strong objection? If you are paying for a quick review, why not pay for post-marketing review?

Mr. FRANSON. Well, I think to go back to the understanding of PDUFA, it was specifically constituted in order to provide FDA additional resources they did not have in order to accomplish the review process. If that scope is going to be expanded, I am sure we would be more than happy to participate in the discussion and construct of that.

Mr. STUPAK. So if we try to change that law in PDUFA III I guess we would be going to now, you would be wiling to at least entertain that idea?

Mr. FRANSON. I think we would be willing to discuss whatever all parties would see as being within the interests of public health.

Mr. STUPAK. Would you be also interested, would the pharmaceutical companies be interested and lend their support in forcing of Phase IV agreements?

Mr. FRANSON. I believe the enforcement of Phase IV agreements is already part of the prior FDAMA, or at least has been introduced as tracking.

Mr. STUPAK. Okay. Well, not quite. Okay. Do I still have time?

Mr. WHITFIELD [presiding]. You are 2 minutes over.

Mr. STUPAK. I have got a lot of questions. I didn't even get to labeling yet.

Mr. WHITFIELD. Mr. Stupak, you are a couple minutes over.

Mr. STUPAK. I understand. I understand.

Mr. WHITFIELD. So it's my turn now.

Dr. Kearns, FDA claims that proper pediatric labelling can save hundreds of millions of dollars a year. Do you agree or disagree with that assessment?

Mr. KEARNS. I would basically agree. I am not a mathematician in the sense of economics, but if we look at the labeling that's happened in the last 4 or 5 years, of those drugs that have been studied in kids, and if we look at the kinds of the things that are in labelling, imagine that a drug company having adverse event information to the tune of saying that more patients, pediatric patients in a trial on this drug died, now the implications for the medical care provider of that information are incredible. Could that save hundreds of millions of dollars in health care costs? Could it save hundreds of millions of dollars in litigation? I think so. I think it really could.

So the impact of labelling, as I stressed in my comments and in my written testimony, it is hard to attach dollar figures to, but for those who care for children, I think it is a critical issue. We won't see the impact of it early. It is going to take 10, 15 years of continued use with new information before we really know what happened.

Mr. WHITFIELD. Yes, ma'am?

Ms. BEN-MAIMON. I just want to make a few comments, one for the record. I think PhRMA actually made a citizens petition submission about a year, just over a year ago, requesting that the FDA decrease the number of trials being required for pediatric exclusivity, and claiming that the requirements were too rigorous. I think it is probably worthwhile for the committee to take a look at that petition.

In addition, with regard to labeling issues, which was just coming up, that is an issue that has to be dealt with very carefully, especially from the standpoint of generic drugs, because as the labels are changed, if there are exclusivities associated with those labels that even go further than the 6 months, or if there are patents associated with those labels, the generic industry is unable to use the label. Since we are required or would like to use, especially when it comes to safety data and especially safety data in children, we would not want to put out products that had a different label or didn't include that data.

So I think the committee needs to look cautiously when it deals with these labeling changes to ensure that it doesn't actually extend the exclusivity even further than the 6 months that was contemplated by Congress.

Mr. WHITFIELD. Thank you for that comment. I appreciate it.

Would anyone else like to comment on that at all? Thank you very much.

Dr. Kearns, have the 18 pediatric labelling changes approved by FDA so far provided a meaningful benefit for the pediatric population, in your view?

Mr. KEARNS. I think without question if we just use one compound that I mentioned, that Dr. Spielberg mentioned, Midazolam, before the innovator company made an oral formulation, before that was tested in children, that drug was given to kids because it's a very good sedative agent. The way it was given, there were all kind of ways that people would go and take the injectable drug

and mix it in Kool-aid with no stability testing, no understanding of the dose. Many times it wasn't stable. But with a properly made formulation, testing in hundreds of children, defining the dose, as we said before defining a safety profile, that drug is probably used 100 times every minute in the United States in pediatric practices. Not just hospitals, dental offices, in any kind of doctor that you can imagine that needs to do a procedure on a child. That is just one example. So without question.

Mr. WHITFIELD. Well that is a good example too. Thank you.

The Tufts Center for the Study of Pediatric Development found that without this exclusivity provision, that pediatric sales market itself was insufficient to render the resources needed to study drugs in children. Now could you compare and contrast for the committee the interests in pediatric studies prior to and after the passage of the exclusivity provision?

Mr. KEARNS. I think in terms of the academic community in pediatrics, and in particular pediatric clinical pharmacology, the interest has always been there. In fact, the work has been there.

If you look at the published literature, there is information. We sometimes forget that pediatricians like Dr. Gorman or Dr. Spielberg didn't use these medicines, you know, on a whim. There are published information about them. That has profiled the use. But it is not generally available. Many times that information comes from uncontrolled settings. So making it formal, putting it under the aegis of the FDA, giving a construct that we know and have known for decades works for adults, makes children their therapeutic equals.

There was a comment or two earlier, and I forget who made it, about the issues of money and somehow it all gets down to money it seems like, about would it be better if the money was given to NIH and NIH studied those drugs or this side or the other. Let me tell you as somebody who has been working for a couple decades doing this and an NIH-funded investigator, the National Institutes of Health is not equipped to do these studies of children. They are not equipped. The Food and Drug Administration has been very helpful and very innovative. But when we look at some of the negotiation and what goes on, there is not the kind of talent at the agency that there needs to be at the agency, in part, limited by funding.

So if we want to do some funding things, let's make user fees available to support the Office of Pediatric Therapeutics at the agency. Let's put some money into the infrastructure to create the kind of expertise across all of government that will not just make this process work, but make it work better.

Mr. WHITFIELD. Yes, sir.

Mr. SPIELBERG. I would echo Dr. Kearns comments. Indeed, the real necessity for having pediatric expertise on all sides within industry, certainly within the FDA, to be able to produce the kinds of written requests that act in the public health interest.

I think one of the interesting contrasts before and after, you know before the legislation, several of the drugs that were labelled now, if you look back at old pediatric handbooks and textbooks, the doses were wrong. The new information that we now have has provided correct doses, both to produce efficacy as well as to decrease

side effects. That is exactly the kinds of information that we wanted from this act, and it has produced it.

Mr. WHITFIELD. Good. Good. Thank you very much.

I recognize Mr. Wynn for 5 minutes.

Mr. WYNN. Thank you, Mr. Chairman. Unfortunately, the Energy Subcommittee was meeting at the same time dealing with the California crisis, and I didn't get a chance to hear the panel's testimony, so I have got some reviewing to do in the meantime. I would like to yield to my colleague, Mr. Stupak, the balance of my time.

Mr. STUPAK. Okay. Thanks to the gentleman for yielding because I do want to ask some questions on labelling. You both made some good points on labelling, especially in pediatrics on how, you know, you've got the doses that were wrong. We learned from it. There have to be changes. But whether it's adult or children, why then does it take so long to get a labelling change? I mean if you look at it and you talk to the FDA, they say they have to negotiate all these changes. If it is so critical that the changes be made, why do they have to negotiate with the companies? Why wouldn't we get it out there immediately?

Mr. FRANSON. If I may respond. Usually labeling is the final step in a review process of an application. Therefore, the industry and the FDA discuss the scientific attributes of a product. Then there is labelling.

In my experience, the discussion takes days, not months, and that it represents the caboose on the train. The delay that may be perceived here is that pediatric exclusivity is granted at a period as defined by the act much sooner than the end point for the review time. So what people see as a lag is merely the execution of exclusivity which occurs by legislation before the end action letter and labeling. It is not our experience that labeling is dragged out.

Mr. STUPAK. Really? I'll be happy to share with you examples, some of them even 2½ years before the label is changed. Two-and-a-half years. These are drugs where deaths were resulting, and 2½ years. That is insane.

Now after you make your label change, okay, let's say you make a label change. What responsibility then is it on the pharmaceutical company, if there is a label change, to recall the drugs that are out there, prescriptions that are out there sitting on the shelves? Is there any requirement to withdrawal? What is the usual course of business then? Let's say you make that label change and the other drugs are out there, distributed all over the United States. What requirement or responsibility legally, ethically, or morally does a pharmaceutical company then have to get the new package out there with new labelling or to doctors, to consumers, and everyone to see?

Mr. FRANSON. That would depend entirely on what the contents of the label change are. There are some label changes that are a formulation.

Mr. STUPAK. How about one that says that due to experience with this drug that death may be associated with it. Now that's a pretty serious consequence. So what requirement then is there on the pharmaceutical company to recall or reclaim those packages that are out in the United States?

Mr. FRANSON. I think the responsibility is on the entire healthcare system, inclusive of the sponsor, to immediately get information on new safety changes to practitioners, practitioners being both pharmacists and physicians. In those cases where some of us have had experience with making such informational blasts, they may take the form of broad electronic plus written, and in some cases even direct contact, hospital formulary groups, and those which keep compendia of medical information are also contacted.

Mr. STUPAK. Does the pharmaceutical company ask for the pharmacists or the doctor's office to return and they will replace their samples, not samples but their supply?

Mr. FRANSON. It would be important to separate the fact that if a new adverse event, for example, is observed, that does not mean the drug product is in any way flawed. It means there is new information associated with it.

Mr. STUPAK. Well significantly enough to negotiate a label change and eventually to put all the dear doctor letter and a Med Watch and everything else. So I mean I can't say that the drug itself is the sole cause, but certainly it is a significant contributing factor to the death of this individual or whatever it might be, the adverse reaction.

Mr. FRANSON. We think it is very important to provide the information to those who need to have it, who are doing the prescribing. As to your analogy, would we ask everybody to drive their car back to the factory to replace an important part, I think that would depend on the situation.

Mr. STUPAK. Yes. We usually get recall notices, right? So at least then the consumer knows that that product at least is being recalled and takes that precaution. Some recall notices say you have to get it in right away. Others say come in, we'll order the part and we'll take a look at it. At least there is some notice given to the consumer, and at least there is a chance to rectify the situation. So I was wondering if the same analogy would apply to labelling.

Mr. FRANSON. I misunderstood earlier. In response to your question, actually when situations of this sort occurs, FDA has a scaled, if you will, escalation process based on the level of severity of a finding. A company would discuss with the FDA whether something necessary needed to be done, anywhere from correspondence to a recall. So again, depending on the situation, that could be one of the possible outcomes, a recall.

Mr. WHITFIELD. Mr. Stupak, your time is up. We are going to be submitting additional written questions, and we would be happy to include any that you might have as well.

Mr. STUPAK. Sure. I thank the gentleman for yielding.

Mr. WYNN. Mr. Chairman, could I just inquire? How many days will we have to submit written, because I think I would like to submit written questions. About how much time?

Mr. WHITFIELD. A couple weeks.

Mr. WYNN. A couple weeks? Thank you very much.

Mr. WHITFIELD. Ms. Ben-Maimon, you were going to make a comment but you were not able to. Do you want to?

Ms. BEN-MAIMON. Very quickly. I think from the standpoint of labeling, I would like to bring it to the attention of the committee

that labeling negotiations actually begin during the development process. Much of the time spent during development is not only to prove safety and efficacy, but to negotiate or to ensure that the outcome, the kind of label that will appear on the bottle, is what you desire.

I think that is important when you look at R&D dollars, that you realize that much of the money being spent is to be in a position to be able to negotiate your labelling, such that you have the outcome that you desire.

Mr. WHITFIELD. I might make a comment that when I said 2 weeks, we want the replies back then. We want the questions going out by next Wednesday.

Mr. WYNN. Thank you.

Mr. WHITFIELD. Mr. Deal, do you have any questions?

Mr. DEAL. More of an observation. I understand the difficulty with which everyone has to deal with this entire subject matter. Certainly the questions and comments that we have heard indicate some of those concerns. I have had an experience recently with a very good friend of mine, a constituent, who is on the other side of the issue. That is, wanting to know why all of a sudden a drug that she considered to be a lifesaving drug was withdrawn from the market, a situation in which maybe a discussion between whether it was voluntarily withdrawn by the company or perhaps done so at the insistence of the FDA.

But be that as it may, and it's in a negotiation process on that particular drug. It appears from all of the information that I have been able to gather with regard to this particular drug, it involves the bad effects, the results that were not favorable—I think maybe a death occurred—were probably prescribing the drug for patients who did not really meet the criteria for which the drug was intended.

I know that is a very touchy and sensitive area as to what pharmaceutical companies can do to fully educate the medical community as to what is an appropriate condition for which the drug is to be prescribed to avoid those kind of situations. But it is unfortunate on two counts. It is certainly unfortunate on the bad experiences that result from the medication having a contrary result. But it is likewise disastrous for those who have had very good results from it and have no other alternative drug on the market, to have that drug suddenly withdrawn from them. The most pathetic situation that I have seen in a very long time, of a woman who is now down to 71 pounds, feels that her life is ruined, and the drug is gone.

So as someone who has seen the other side of the constituent concerns about drugs that are perceived to be very beneficial, but are suddenly withdrawn, I would just simply add my concern and my encouragement that when these kinds of cases arise, to try to resolve those as quickly as possible, because there are those who are depending on those drugs and have a very difficult time understanding why once a salvation had been provided, it is now taken away from them. That is the most recent constituent concern that I have encountered.

So there are certainly very many facets to all of the things that all of you deal with. I think we all appreciate that fact.

Mr. BILIRAKIS. Would the gentleman yield?

Mr. DEAL. Yes, I would.

Mr. BILIRAKIS. Is there any adequate remedy available for that woman? No exceptions? Any comments on that? Should there be? Should there be something in the law that would afford that person, that type of individual the opportunity to continue to use this withdrawn drug?

Mr. FRANSON. I would comment that there are very special circumstances that go through FDA approval processes that allow compassionate use access to drugs, and that there are other agreements that may be reached. They are on a case-by-case basis.

Ms. MEYERS. Often when that happens, FDA will tell the company to put the drug back on an IND, which is an investigational new drug. It becomes experimental again. These patients, we have known patients for example with epilepsy drugs that were withdrawn from the market that have taken them for the following 10 years, as long as the company agrees.

Now barring that, let's say the company does not agree, if the drug is approved in Europe the FDA has a regulation for individual importation of drugs. If you have a prescription, you can get up to 90-day supply and order it from a European pharmacy. So if it's in another country, American consumers can get it.

Mr. BILIRAKIS. Is it conceivable that that drug may be available?

Mr. DEAL. Well, I don't mention the names, et cetera, and the reason being that I think the negotiations are in the very final stages of working out an agreement to get the drug back on the market with maybe more restricted labelling. I certainly don't want to do anything to jeopardize that or to prejudice anyone's opinion in that regard. But I did ask those very same questions.

Those options did not appear to be available simply because they thought a broader option was available once the negotiations were concluded. Now if the negotiations are not successful in a relatively short timeframe, I am going to have a constituent who is going to be asking for those kind of optional remedies, at least—because I asked the same thing. I said well why can't somebody who has had a very good result and who wants to proceed with the use of the drug not have the ability to do that. So some of you may hear from me again if negotiations don't go very satisfactorily.

Mr. BILIRAKIS. Yes, Dr. Kearns?

Mr. KEARNS. Thank you. If I could just make a quick comment. This has to do with post-marketing data and decisions. If during the course of a clinical trial a serious adverse event becomes apparent, it is fairly easy to make decisions about whether a drug needs to go on or not. But in the post-marketing period, it is very, very difficult, especially when we are left with a reporting system that's voluntary.

At a recent NIH conference about 3 weeks ago, a presentation was given that said physicians report on average about one adverse event every 350 years. This was data given by a person who is a pharmaco-economics person. I can't verify the source of it. But in a spontaneous reporting system, all we have many times are numerator data. We don't have the denominators. Looking at the descriptions of those adverse events sometimes are laughable, but yet they register on the radar screen of the agency who with its charge

to protect the public will often times start the initiative for decisionmaking.

I believe as a professional, that part of our system really does need some fixing. We really have to have good data. We need good drugs on the market that help people. We don't need to throw the baby out with the bath water. But at the same time, we need to know when we've got a drug that maybe made it to market, and because of an effect that we couldn't see in the clinical trials of a couple hundred patients, that we can prudently act to protect society.

Mr. DEAL. Thank you, Mr. Chair.

Mr. WHITFIELD. I want to thank the panel very much for your patience and your time. We all enjoyed your testimony very much, and we look forward to working with you as we continue to deal with this issue.

Remember, next Wednesday, questions must be in. We hope in 2 weeks they will be——

Mr. BILIRAKIS. Not only questions in, but just the point raised by Mr. Deal. If there are any areas where you feel, you know, if you were king, you would change or at least suggest changed, you have got the opportunity to do that. Submit all that information to us.

Thank you very much.

[Whereupon, at 1:59 p.m., the subcommittee was adjourned, subject to the call of the Chair.]

[Additional material submitted for the record follows:]

PREPARED STATEMENT OF ADVANCED MEDICAL TECHNOLOGY ASSOCIATION

I. INTRODUCTION AND SUMMARY

The Advanced Medical Technology Association (AdvaMed) is pleased to submit the following testimony on the implementation of the Food and Drug Administration Modernization Act of 1997. AdvaMed is the largest association of medical technology innovators in the world, representing more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. Two thirds of AdvaMed's members are small businesses, and the vast majority of those firms have 50 or fewer employees. Our members manufacture nearly 90 percent of the $62 billion in health care technology products purchased annually in the U.S. and more than 50 percent of the $147 billion in health care technology products purchased worldwide.

AdvaMed would like to express to the members of this Committee our thanks and appreciation for making your vision of modernizing FDA laws a reality, and passing the "Food and Drug Administration Modernization Act of 1997" (FDAMA). Further, AdvaMed is pleased to have the opportunity to discuss some important aspects of that legislation for the medical device industry, and the triumphs and difficulties in its implementation. Also, we would like to share AdvaMed's views on ways to develop the central goals of FDAMA including FDA's mission to not only protect but to promote the public health, in the way Congress intended.

This hearing occurs at a critical juncture for FDA. America stands on the cusp of a revolution in medical technology. As was highlighted by members of FDA's Science Board at a meeting April 13, many emerging breakthroughs—such as tissue-engineered technologies and drug/device combinations—will not fit easily into FDA's existing regulatory framework. The agency faces a significant challenge in effectively overseeing development and approval of novel medical technologies in the coming years.

AdvaMed believes it is critically important for FDA, Congress, and medical technology companies to work together to prepare the agency for the coming revolution in medical technology and promote timely patient access to lifesaving and life-improving medical technologies.

Today's hearing is an important first step towards that goal. To prepare FDA for the future, we must first look back to ensure that FDAMA's legislative changes have been fully implemented and are achieving their goals.

- For example, FDAMA helped to streamline the premarket review process by permitting FDA to "recognize" national and international consensus standards through publication in the *Federal Register*. Because FDA has recognized a large number of such standards, persons who submit 510(k)s and PMAs often can submit declarations of conformity to applicable standards instead of reams of data demonstrating conformance to a standard. This process shortens the time it takes to effectively review a premarket submission, results in prompter review decisions, and holds persons accountable for their declarations by requiring them to maintain for FDA the data upon which a declaration is made.
- FDAMA embodied the important goal of increased collaboration between industry and the FDA. The law created several meetings to address premarket submission issues and required FDA to include stakeholders in the process of assessing and recommending regulatory improvements. Although the effectiveness of meetings in reaching agreements on data necessary to achieve market approvals needs work, the agency has been willing to listen to our concerns. Additionally, there have been stakeholder meetings, and a continuation of that process to capture the thoughts from scientists, physicians, consumers and industry will surely benefit FDA as it attempts to modernize its regulatory process.

These provisions are but a few that show how FDAMA changed the law to achieve the goals of public health protection, greater collaboration, and more efficient regulation. Although significant progress has been made, there remain areas for improvement. For example, for the last 3 years, the average total elapsed review times for PMA submissions remain at about 12 months—nearly twice the statutory review time of 6 months—even though many of the FDAMA provisions were intended to streamline PMA reviews. AdvaMed recommends a few fixes to FDAMA that may be helpful, as well as suggest changes in the law to help prepare and support FDA for the continuing challenges presented by rapidly developing health care technology.

II. FDAMA HIGHLIGHTS.

Expanded Access to Investigational Therapies & Diagnostics

FDA has implemented a number of FDAMA provisions effectively and the public has benefited as a result. Through reliance on FDAMA, the agency has achieved benefits for individuals with significant need for expanded access to unapproved and life saving technologies. Specifically, FDAMA provided persons who need new technologies for treatment access to investigational devices when various statutory conditions are met. Additionally, FDAMA facilitated the effectiveness of the law's humanitarian device provisions to ensure that patients in need of these orphan devices have the earliest access to them possible, and the agency has done well in implementing this provision. Further, FDA has effectively implemented FDAMA's requirement for 30-day notices instead of 180-day premarket reviews for certain manufacturing changes. Each of these agency efforts has resulted in benefits to the public.

The expanded access provisions include emergency, compassionate and treatment use of devices. This authority complemented authority in FDA's regulation to allow deviations from an IDE when necessary to treat patients in substantial need. While emergency use does not require prior FDA approval, compassionate and treatment use do. Compassionate use can accommodate small groups of persons who need investigational devices. Treatment use permits the more widespread availability of investigational devices. Both of these latter means of expanded patient access to investigational products require approved IDEs. FDAMA and FDA's regulations describe criteria for such expanded access, including that there are no available and satisfactory alternative treatments. FDA has been reasonable in administering these provisions; indeed, the agency demonstrated enthusiasm in "getting out the message" about these new means for patients to gain access to new and advanced therapies. Within sixty days of FDAMA's passage, FDA published a document entitled "Guidance on IDE Policies and Procedures" that explained the agency's implementation of its investigational device authority, including discussions of how the new provisions added by FDAMA complemented existing IDE procedures.

Expanding Humanitarian Use of Devices

Consistent with its endorsement and support of expanded access, FDA has been responsive to FDAMA's amendment of the Act's humanitarian device provision. Since 1990, FDA has had authority to approve devices for uses in treating conditions that affect fewer than 4,000 individuals, on the basis of safety information alone. In a sense Congress created an orphan device provision and modified the effectiveness requirement for humanitarian devices. This change reduced the substantial cost of developing a device, thus providing an incentive for manufacturers to de-

velop devices that otherwise might never be brought to market because of small demand. To further ensure that humanitarian devices are developed for persons who desperately need them, FDAMA reduced the review period from 180 to 75 days. Although FDA's annual device reports show that final humanitarian device decisions are taking longer than 75 days, clearly the agency is being responsive to the FDAMA requirement and has reduced the overall time for HDE reviews.

Manufacturing Changes

FDA's success in the humanitarian device area is also seen in the agency's implementation of FDAMA's manufacturing notice provision. This provision greatly reduces the regulatory delay that accompanied FDA's review of manufacturing change supplements. Now instead of submitting such supplements for potential 180-day reviews before a change could be implemented, manufacturers can submit 30-day notices for a broad array of manufacturing changes. Once thirty days have passed, these proposed changes can be put into effect, unless FDA notifies a manufacturer that there is a need for a PMA supplement. After FDAMA's enactment, FDA promptly issued its guidance document describing how this notice provision would work. A large number of notices have been received and reviewed by the agency without delays, clearly demonstrating the clarity and industry's understanding of FDA's manufacturing notice program.

AdvaMed's members and the public have benefited greatly from the agency's successful implementation of the notice provision. FDA is not tied up with unnecessary resource intensive reviews that require approvals, and manufacturers can keep their manufacturing processes as efficient as possible without waiting for lengthy periods of time while their manufacturing supplements work their way to the head of a review queue.

The implementation of every provision of FDAMA hasn't been as smooth. A number of key FDAMA provisions, which have substantial potential to modernize device regulation, have had an uneven implementation experience.

Least Burdensome

Two critical provisions in FDAMA require the agency to only require that information necessary to approving a PMA device or clearing a 510(k) device, and to consider the "least burdensome" information in determining premarket approval or clearance requirements. Essentially what this means is that FDA should not require a randomized, double blind prospective clinical study if a partially controlled clinical trial would provide the statutorily required reasonable assurance of safety or effectiveness.

The agency hasn't always agreed with this view. Initially after the enactment of FDAMA, it was very difficult to engage the agency in a discussion of the least burdensome concept. Typically, AdvaMed members were confronted with randomized clinical trials as the agency's expression of the least burdensome showing to establish device effectiveness. Seldom was there even conversation about least burdensome in the context of substantial equivalence. This concerned me because it suggested a regulatory "cultural" bias within the agency that was resistant to Congress's direction of avoiding over-regulation. In response, AdvaMed and others developed a document to define "least burdensome" in order to place the issue before FDA to encourage a collaborative exchange with an eye toward a regulatory guidance document. This document, after some resistance from the agency, achieved its purpose. FDA and industry started to talk and made headway in describing and defining the least burdensome concept. This effort has resulted in some least burdensome principles as a starting point for thought and discussion:

- The spirit and the letter of the law should be the basis for all regulatory decisions;
- Information unrelated to the regulatory decision should not be part of the decision-making process;
- Alternative approaches to all regulatory issues should be considered to optimize the time, effort, and cost of reaching proper resolution of the issue; and
- All reasonable mechanisms to lessen review times and render regulatory decisions within statutory timeframes should be used.

We were very encouraged when, two days ago, the agency issued its guidance document on the least burdensome concept and principles and that the agency clarified that the least burdensome concept applies to all devices including in vitro diagnostics (IVDs). AdvaMed also believes that the above collaboratively derived principles already have had a positive effect on the agency.

However, our experience with FDA in trying to implement the least burdensome provisions underlines an important fact. To modernize device reviewers' approaches to premarket submissions requires a cultural change at the agency.

We have no doubt that Americans will look back on Congress' decisions to double the research budget at the National Institutes of Health and unravel the human genome as two of the smartest investments yet made in this new millennium. We must be equally sure that the FDA and other regulatory bodies are prepared to handle the increasing number and complexity of resultant innovations—like combination products' with an efficient, clear and predictable pathway to approval. To accomplish this goal, device reviewers need more opportunities to discuss submission issues with industry and to interact with outside scientific and medical experts to bring fresh perspectives into the device review arena. Consistent with the agency's mission of promoting patient access to new technology, requesting the most demanding clinical information is not always the best way to demonstrate safety and effectiveness of new and complex technologies. This has too often been the FDA approach.

Early Collaboration Meetings

Congress was acutely aware that collaboration between potential premarket submitters and FDA would add efficiency to the premarket review process. To ensure collaboration, two FDAMA provisions were included in the law, both resulting in binding requirements on FDA. Effectively, a first meeting ("determination meeting") required FDA to determine the least burdensome type of information—ranging from bench testing to clinical studies—necessary to demonstrate device effectiveness. The second meeting ("agreement meeting") permits the potential applicant to submit device investigation plans, including clinical protocols for FDA's review and possible agreement. Any agreement reached at the meeting would be binding.

Congress summarized the importance of these two types of meetings, stating the provisions were intended

> to provide for a predictable structure through which the FDA and sponsors of applications for marketing of new products can communicate effectively regarding requirements that must be met to secure marketing clearance or approval. The Committee believes that meetings between the appropriate FDA experts and their industry counterparts may provide one avenue to successful communication that may result in agreements that can expedite a manufacturer's understanding of what information, data, or investigations may be needed for a particular product.
>
> *(H.R. 307, 105th Congress, First Session, 1997, at 26)*

The effect of a successful implementation of these meetings should be substantial resource savings for companies and the FDA and the prompter delivery of new, safe and effective devices to consumers. Without question, a mutual understanding of devices and device requirements will ensure the most efficient and effective reviews.

So far, this goal has not been realized. FDA's actions have shown a continued preference for informal meetings that do not result in binding outcomes. Although the agency is trying to improve its approach to these pre-IDE meetings, the number of binding outcomes still pales by comparison to the number of IDE submissions that pass through the agency. Active discouragement of these meetings by FDA reviewers has affected the willingness of companies to request them. Both industry and FDA must constructively address this situation.

Third Party Review

Another FDAMA provision that's very important to our members calls for review of 510(k)s by expert third parties outside the agency. Under this provision, accredited third parties review 510(k)s and make recommendations to FDA about device clearances. FDA has 30 days to consider such recommendations and to issue a 510(k) decision. Originally, FDA limited the program to product types having a specific guidance document. Typically, these products were the simplest devices and were associated with rapid reviews. We are encouraged that FDA has recently expanded the list of devices eligible for third party review, and believe that this expansion that now includes more complex devices was necessary to encourage greater utilization of the program.

Dispute Resolution

Implementation of FDAMA's scientific dispute resolution provision initially began slowly. This part of the law required FDA to promulgate a regulation establishing a procedure for requesting review of scientific disputes between sponsors, applicants, or manufacturers and FDA by a scientific advisory panel. At first, the agency issued a complicated guidance document, detailing a dispute resolution procedure and explaining all the review mechanisms that already exist in the statute and regulations. Since then, however, the Device Center has appointed an ombudsman, and the ombudsman has been actively soliciting persons to use his office if disputes or

other matters surface that require an intervenor. This effort to provide industry and others a voice within the Center is promising and we appreciate the effort being made to create a reasonable dispute resolution process. Nevertheless, a cultural change is needed at the agency to ensure that the dispute resolution process is fully implemented as Congress intended.

III. THE FUTURE

We have seen significant accomplishments by the agency in its efforts to modernize, both by successfully implementing several FDAMA provisions, and reengineering a number of its programs. But we know that the agency must do more to meet the challenges of unprecedented growth and rapid evolution in medical research and technology. In a report on the "Outlook for Medical Technology Innovation" issued by the Lewin Group, medical device manufacturers have doubled their R & D spending to bring these innovative technologies to fruition. As this trend continues, the agency must be made ready to meet the challenges associated with the unprecedented growth in the industry.

Many provisions of FDAMA equip the agency with the flexibility to conserve its valuable resources such as the third party review program. Industry's use of this program has been limited because more complex devices whose review would benefit most from a third party are currently ineligible for the program because of statutory restrictions. AdvaMed supports the third party review program and would like to see it used by industry to the fullest extent possible. However, with the current eligibility criteria, we are concerned that Congress's belief that third party review will assist FDA's premarket review program will go unfulfilled.

The intent of FDAMA's expedited review provision was to ensure that breakthrough devices reach the market as soon as possible. The public health demands this result and we support any effort that would enable the agency to ensure that breakthrough devices receive review queue and review resources priority.

Combination products continue to present challenges to the agency's standard review mechanisms, resulting in inefficiency and delay. Although FDAMA streamlined many of the agency's review processes, the legislation did not address the difficult issues that arise when devices incorporate drugs or biologics and the efficient review of these combination products. Because of the unsatisfactory experience many AdvaMed members have had when devices are reviewed by other Centers or combination products are assigned to the Device Center with consultative reviews from CDER or CBER, we recommend creating an Office of Combination Products and Product Jurisdiction. The Office would identify a Center with regulatory responsibility for a product based on the product's "primary mode of action." Additionally, the Office would ensure the product reviews are timely and, if more than one Center is involved in a product review, that reviewers assigned to conduct the review would be under the authority of the Office Director. Only through increased oversight by an independent authority within FDA do we believe that combination products, containing devices, will receive efficient and timely reviews

IV. CONCLUSION

AdvaMed appreciates the opportunity to provide comments on the implementation of FDAMA. FDAMA created the framework to reform and modernize FDA's practices and procedures. The record of its implementation is somewhat inconsistent, with examples of aggressive efforts by the agency to realize most goals of the legislation, and a few implementation shortfalls that need attention. On the whole, AdvaMed is heartened by FDA's positive approach to discussing issues, and we believe that with increased collaboration between the agency and industry significant progress is still in the offing.

At the same time, AdvaMed believes that to avoid increasing delays in the FDA review process, it is critically important to consider what steps must be taken beyond the FDA Modernization Act to prepare FDA for the technologies of the future. AdvaMed looks forward to working constructively with FDA and Congress to achieve this goal and ensure timely patient access to the emerging breakthroughs in medical technology.

PREPARED STATEMENT OF FRANK CLEMENTE, DIRECTOR, PUBLIC CITIZEN'S CONGRESS WATCH

Chairman Bilirakis and Ranking Member Brown, my name is Frank Clemente and I am Director of Public Citizen's Congress Watch. Public Citizen is a 150,000 member national consumer group, which is active on a wide range of issues includ-

ing health care. For 30 years we have been a leading watchdog of the Food and Drug Administration (FDA) and the pharmaceutical industry on issues such as drug safety and drug pricing.

I want to thank you for the opportunity to comment on reauthorization of the pediatric exclusivity provision originally enacted in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA). In order to provide a context for our views on reauthorization of pediatric exclusivity, let me first present to you the prehistory of this provision as discussed in a recent report by the FDA.[1]

In these comments I will be using the term "labeling" in its technical regulatory sense, which refers to the information about the uses of a drug that appear on the packaging of a drug. Labeling of prescription drugs is strictly controlled by the FDA. Manufacturers may only make a claim that a drug can be used for a particular ailment if the manufacturer has shown, based on sound science and to the satisfaction of the FDA, that a drug is safe and effective for the indication in question.

The problem of a lack of labeling for children has been recognized for over two decades. According to the FDA, in 1973, 78% of the drugs listed in the PDR lacked sufficient pediatric labeling. In 1991, 81% of the drugs in the PDR lacked adequate labeling. As recently as the early 1990s, drug companies were doing little to assure that drugs are adequately labeled for use in children. From 1991-1994, 71% of the new molecular entities coming onto the market lacked pediatric labeling. According to the FDA, the lack of pediatric labeling information "poses significant risks for children." In its proposed rule on pediatric studies issued in 1997, the FDA cited reports of injuries and deaths in children resulting from the use of drugs that had not been adequately tested in the pediatric population.

In 1994, the FDA issued a rule requiring drug companies to do a review of the scholarly literature and to submit a supplemental new drug application if studies were available to support labeling a drug for use in children. In 1994, the FDA also started a voluntary plan designed to encourage drug companies to gather data on pediatric use both during drug development and after marketing. According to the FDA, both these efforts met with only limited success.

Between 1991 and 1996, drug companies did little to deal with the problem of drugs already on the market that lacked adequate labeling about use in children. They promised to conduct 71 post-marketing pediatric studies, but only 11 (15%) were completed in that period, according to the FDA.

In 1997, the FDA began the process of enacting regulations to require drug companies to test drugs in children for the labeled adult indication as a condition of a drug's approval by the agency. In 1998 the pediatric rule was finalized. Under the rule, drug companies are allowed to seek a waiver of the requirement to test a new drug in children if they believe that it will not be used in children. Currently, the rule is tied up in court by legal claims that the FDA does not have authority to issue it.

In 1997, before the pediatric rule was finalized, Congress responded to the poor results of previous efforts, by passing the pediatric exclusivity provision as part of FDAMA. Pediatric exclusivity grants drug companies 6 months of additional patent exclusivity if they conduct studies of drugs in children that the FDA determines will provide physicians with useful new prescribing information. The result was a dramatic increase in the number of pediatric studies being done by the brand name drug companies. From the time the FDA issued a guidance in 1998 to September, 2000, over 191 proposed study requests were submitted to the agency, 58 had been completed, 25 drugs had received grants of exclusivity, and the drug companies had made labeling changes on 12 drugs, less than half of those that have received pediatric exclusivity.

PROBLEMS WITH THE PEDIATRIC EXCLUSIVITY PROVISION

Mistargeted

While the incentive offered to drug companies by the pediatric exclusivity provision of FDAMA has been successful in increasing the number of studies done and has provided valuable information to pediatricians about how to use drugs in children, the law as it currently stands is poorly targeted. It offers drug companies:

- Substantial incentives to test drugs that have high sales, particularly among adults, not those about which pediatricians most need more information. Currently brand name drug companies are receiving 6 months of exclusivity (effectively a patent extension) for testing a drug on children, even when that testing

[1] Department of Health and Human Services, Food and Drug Administration, *The Pediatric Exclusivity Provision: January 2001 Status Report to Congress.*

is of minimal value, because it is for an indication that rarely occurs in children, such as ulcers, hypertension, or type II (adult-onset) diabetes.

- Little incentive to test drugs that are still under patent but not big sellers. Pediatric exclusivity leaves many drugs unstudied in children, because the drug companies believe they will not make enough from 6 months of additional patent protection.
- No incentive to test drugs that are currently off-patent. Six out of ten of the drugs most widely used in children without adequate labeling are not eligible for pediatric exclusivity, because they are off patent. One example of such a drug is ampicillin, which is used to combat infection in children.

Substantial cost to consumers

As a consequence of the pediatric exclusivity provision, consumers are denied access to lower-priced generic drugs for an additional 6 months. The cost this imposes on consumers is substantial, as is the corresponding windfall for brand name drug companies. Over the course of the program's first 20 years, the FDA estimates that the cost to consumers will be $13.9 billion. *The Wall Street Journal* recently estimated that pediatric exclusivity will add $4 billion to brand name drug company revenues, and this is just for the first 26 drugs tested under the program.[2] Who bears the burden of pediatric exclusivity? Overwhelmingly it is the elderly, who use more prescription medications than the young, and only about half of whom have reliable year-round prescription drug insurance. It is the uninsured who pay the highest prices for prescription drugs, the full retail price, because they do not have access to the lower prices negotiated by large purchasers such as HMOs and hospitals.

Windfall to drug companies far exceeds the costs of conducting studies

The windfall to the drug companies in the form of higher revenues as a result of the longer monopoly period provided by pediatric exclusivity is almost always significantly greater than the cost of the studies that the drug companies must do in order to be eligible for exclusivity. *The Wall Street Journal* estimates that pediatric studies cost anywhere from $200,000 to $3 million each. This is much less than additional revenues drug companies will earn as a result of exclusivity, particularly for blockbuster drugs. If you assume, as The Wall Street Journal does, that a brand name drug's sales decline by 75% after the introduction of a generic, and you look at the two most outrageous examples this is what you find: For testing Prozac in children, Eli Lilly received 6 months of additional exclusivity, worth $964 million, more than 300 times the cost of doing a study (assuming $3 million per pediatric study). Schering Plough received exclusivity worth $575 million, more than 150 times the cost of doing a study for testing its blockbuster drug Claritin in children.

While the drug industry is entitled to make a good profit, such windfalls from pediatric exclusivity are clearly excessive and unnecessary. As a whole the drug industry, consistently the most profitable for the past 10 years, can well afford to bear the cost of doing pediatric studies without any additional incentives. It had $192 billion in sales last year; the top 12 companies had combined profits of $28 billion—an incredible 19% return on revenue. Merck, the industry's highest seller, recorded sales of $40.4 billion and profits of $6.8 billion in 2000. Clearly, this is not an industry that needs additional corporate welfare to compensate it for the cost of doing a few million dollars of testing in children.

SOLUTIONS

Given the problems with the current law, Public Citizen urges the Committee to enact the following legislative changes:

For new drugs used for an on-label indication in children: Codify the FDA's pediatric rule to require testing of these drugs and end pediatric exclusivity for this testing.

By codifying the rule, FDA's authority would be clarified and testing of new drugs that will be used by children for a labeled adult indication would be assured.

Once FDA has this authority, there no longer would be a need to give drug companies 6 additional months on their patent and force consumers to pay higher prices for their drugs as a way of enticing the companies to test drugs on children.

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[2] Rachel Zimmerman, "Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids" *The Wall Street Journal,* February 5, 2001.

For drugs still on patent but used for an off-label indication in children: Pediatric exclusivity should be used as an incentive to encourage the testing of these drugs in children.

The FDA does not have authority to require companies to test for uses in children or adults that companies have not sought FDA approval for at the time a drug was originally approved (off-label uses). Therefore, it will be necessary to provide incentives to encourage drug companies to do such testing. For drugs used off-label we recommend the following more targeted and greatly reduced incentives:

- **Scale the length of exclusivity to the sales of a drug.** As it is currently structured, pediatric exclusivity offers a windfall to drug companies when it is granted to a blockbuster drug with high sales income. Drug companies should receive the same incentive for testing all drugs that qualify for exclusivity. This can be done by granting fewer days of exclusivity to drugs with high sales income and more days of exclusivity to drugs that have lower sales income. Congress should set the value of exclusivity that all qualifying drugs would receive in legislation.[3] This value should be set at such a level that it is a sufficient but not excessive incentive to the drug companies.
- **Tie the granting of exclusivity to a company making labeling changes.** It is critical to pediatricians that new information gathered from drug company testing be reflected in labeling changes so that they can make the best prescribing decisions. Unfortunately, under current law companies are awarded exclusivity simply upon completing tests in children. Some companies do not pursue the necessary labeling changes in good faith with the FDA, because there may not be a marketing advantage to them. Without a requirement that drug companies make labeling changes in order to receive the grant of exclusivity, there is no way to assure that labeling changes will be made in a timely manner.

For older, off patent drugs: Fund independent centers to do testing in children.

Many drugs that are used in children are older drugs that are off patent. The pediatric rule does not extend to these drugs. And since these older, off patent drugs are often made by many different generic companies, it is not possible to give one company exclusivity in exchange for testing and a labeling change. Also, in the case of many low-selling drugs still on patent, the pediatric exclusivity provision is not an adequate incentive to encourage companies to do studies in children. For these older drugs and low-selling drugs still on patent we urge that funds be made available to the Pediatric Pharmacology Research Units (PPRU) and the Centers for Education and Research on Therapeutics (CERT) to test the effectiveness of these drugs in children. (The CERT centers were created by a provision in FDAMA.) Also, the FDA should require the relevant results of this research to be reflected in labeling changes.

Again, I thank the Committee for the opportunity to testify. Public Citizen urges you to end the substantial giveaway to the drug industry that occurs under pediatric exclusivity. The same goals of the original law—understanding how prescription drugs approved for adults will affect children—can be much better achieved by requiring drug companies to do such testing as a condition of their original new drug application. We can achieve a much better balance between the needs of our children and consumers and those of the drug companies than currently exists under pediatric exclusivity—at a cost to the drug industry that is small in comparison with their overall revenues.

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[3] While there is an incentive in existing law (other than pediatric exclusivity) designed to encourage drug companies to do the testing required to label drugs for off-label uses, the incentive is weak. Under current law, when drug companies do tests on a drug and submit a labeling change to the FDA to reflect a new use for a drug, they receive three years of exclusivity on the new indication. Assuming that a company sought this labeling change at the end of the patent life of a drug, this would mean that the company would have the exclusive right to promote the drug for the particular indication in question for three years after the patent expired on the active ingredient in a drug. This grant of exclusivity is not very valuable to the drug companies, because during those three years if the patent on the underlying active ingredient had expired, generic drug companies would be able to produce and sell a competing drug with that active ingredient, so long as they did not label it for the protected indication. In contrast, under pediatric exclusivity, generic drug companies are barred from selling a drug with an active ingredient that has been granted pediatric exclusivity—a much more valuable prize. It is for these reasons that pediatric exclusivity is needed to give drug companies the incentive to do the testing necessary to label drugs for off-label uses in children.

PREPARED STATEMENT OF ARTHUR COLLINS, CHIEF EXECUTIVE OFFICER, MEDTRONIC

I. INTRODUCTION—MEDTRONIC'S INTEREST IN BREAKTHROUGH THERAPIES

My name is Art Collins. I appreciate the opportunity to provide testimony to the Subcommittee on Health as you assess the effectiveness of the Food and Drug Administration Modernization Act (FDAMA).

I am the Chief Executive Officer of Medtronic. Medtronic is the world's leading medical technology company, providing lifelong solutions for people with chronic disease. With deep roots in the treatment of heart disease, Medtronic now provides a wide range of therapies that help physicians solve the most challenging, life-limiting medical problems and restore health, extend life, and alleviate pain. Therapies are organized in four primary groups—Cardiac Rhythm Management, Vascular, Cardiac Surgery, and Neurological, Spinal and ENT.

Medtronic's 25,000 employees serve patients in 120 countries. Medtronic has scientific, manufacturing, education and sales facilities worldwide. Revenues for the year ending April 30, 2000 were $5.01 billion. Approximately a third of the company's revenue turnover is contributed by its business overseas and about 25 percent of its employees are outside the U.S.

As you may know, Medtronic strongly supported the Committee's important role in developing this legislation. Further, Medtronic is a world leader in developing breakthrough therapies for chronically ill patients. Indeed, our Mission Statement directs us to participate in areas where we can make a unique contribution to human welfare by developing therapies that alleviate pain, restore health, and extend life. As a consequence, we are uniquely situated to comment on FDAMA's support for breakthrough therapies—and further initiatives that might improve this country's ability to bring breakthrough, life-saving technologies to critically ill patients.

As its name states, Congress intended that FDAMA would modernize the FDA's regulatory process. Specifically, the goal was to create an efficient and effective regulatory process that would bring medical products to the patients who need them. FDA has done a good job in making FDAMA work and in ensuring that Americans have access to safe and effective medical devices and drugs.

Today we can build upon the momentum of FDAMA and work to guarantee patient access to breakthrough technologies. These are the novel devices that treat life-threatening diseases or conditions and take longer and are more expensive to develop than other devices. If we keep the central tenets of FDAMA in mind, namely:

- enhanced collaboration between FDA and industry,
- increased certainty in the review process, and
- avoidance of over-regulation

we can forge a path for breakthrough technologies to move them from a biomedical engineer's creative thought to a patient's bedside as efficiently and effectively as possible. I highlight breakthrough technologies because we all can agree on their importance, but we also must recognize the disincentives to their development that currently exist. By modernizing the regulatory process for breakthrough devices we can continue the success of FDAMA, dampen some of the disincentives facing the development of breakthrough technologies, and, most importantly, help Americans in getting the medical care they need.

II. OBSTACLES TO INNOVATION AND BREAKTHROUGH TECHNOLOGIES

We can define a breakthrough device as one that is novel in design, operation, or function, and is intended to treat life-threatening diseases or conditions. I contrast breakthrough devices with "new" devices that are modifications of, or incremental changes to, devices with well-established track records. Because breakthrough devices take longer and are considerably more expensive to develop than those incrementally improved devices, sponsors of breakthrough devices must make a large commitment to the long haul.[1]

I will provide just one example of such a breakthrough therapy recently developed by Medtronic and in various stages of consideration by the FDA and global regulatory bodies. **Activa**® Therapy is the umbrella term describing the medical treatment developed by Medtronic, in collaboration with physician researchers, that uses brain stimulation to suppress the symptoms of movement disorders. The therapy uses an implantable medical device to deliver mild electrical stimulation to brain structures involved in motor control. It includes in particular Activa Parkinson's Control Therapy, which is the most significant advance in the treatment of the disease in more than 30 years. Developed by Medtronic in collaboration with pioneering physicians, the therapy can control the primary motor symptoms of patients

with advanced, levodopa-responsive Parkinson's disease that is no longer adequately controlled with medication. It is an adjustable and reversible therapy that uses an implanted medical device to deliver mild electrical stimulation to either the subthalamic nucleus (STN) or the globus pallidus interna (GPi) to counter the brain signals that cause the symptoms of Parkinson's disease. There is currently no cure for Parkinson's disease and indeed current treatment options have disabling and unpredictable side effects.

Overall, the medical device industry has demonstrated its commitment to the research needed to support such innovation. In fact, the device industry invests a higher percentage of annual income in research and development than other industries.[2] This investment in R&D has only increased in the last decade. Medical technology firms invested 5.4% of revenues in R&D in 1990. By 1998 that figure doubled to 12.9%.[3] The United States is the largest producer of the R&D that leads to new health care technologies and also is the largest market for these technologies.[4]

Despite this commitment to technology and innovation, companies face many barriers in their pursuit of breakthrough devices. Take, for example, the FDA regulatory process, which can create uncertainty and high costs, often from time delays, for manufacturers. FDA's inability today to review efficiently new technologies is understandable; reviewing these technologies requires considerable resources and expertise, two things that the agency today struggles to maintain. For companies with few products, the uncertainty and delays associated with the FDA's role in the product development and approval process can be especially challenging as these companies cannot absorb the extra costs associated with lengthy development processes and untimely reviews. Indeed, the pressures on small companies created by the FDA regulatory process have long been recognized by both industry and government.[5]

Payment obstacles also discourage innovation and force companies to scale back their research and development or market their products abroad first.[6] Health insurers, including Medicare, often have requirements that are higher than the requirements necessary to gain FDA approval.[7] Added uncertainty in the reimbursement process arises for innovative devices. It is more difficult to secure payment for these new (FDA approved) devices, which do not have precedents upon which to rely; compared to incrementally changed devices, which follow more predictable routes to coverage and payment.[8] Innovative devices also have greater financial pressure from Medicare's coverage of devices studied under an investigational device exemption. Medicare may pay for devices that are newer generations of proven technologies for which initial questions of safety and effectiveness have been resolved, but will not cover novel, first-of-a-kind technologies.[9] By raising these points, I do not argue that the reimbursement system is flawed or debate the policies behind the system; instead, my point is specific: obstacles to innovation exist and have significant consequences.

I know that you are aware that small companies suffer the consequences of a delayed regulatory review process and payment hurdles. Currently, the device industry is primarily comprised of small companies, which are often the source of novel devices. Indeed, one study found that start-up firms were disproportionately responsible for the innovation and early development of novel devices.[10] But funding for small companies is hard to come by and venture capitalists, particularly when money is tight, do not want to invest in small companies whose products take a long time to develop, such as medical devices, and who are part of a highly regulated industry, such as the device industry.[11] Indeed, medical devices are not developed cheaply; taking a new device from concept to market can cost $20 million or more.[12]

What may surprise you is that small firms are not alone in feeling the pressures that deter innovation and development of breakthrough technologies. Large firms must respond to their investors who prefer products that have a quicker turnaround time. Incrementally changed devices fit this bill. As I stated before, there is more certainty in their review process, which makes that process shorter. Additionally, with incrementally changed devices the marketing commitment is smaller. For example, a company does not have to sell a doctor on the benefits of a newly modified pacemaker; the doctor is familiar with the technology and will understand the new features. Selling a breakthrough device to a doctor for a disease that the doctor historically has treated with a drug requires much more time and commitment.[13]

To encourage innovation some firms have undertaken creative endeavors, but these endeavors can be risky undertakings and, by far, are the exception and not the rule. I offer as an example, Itasca Ventures, a "venture incubator" formed and operated a few years ago by my company, Medtronic, Crescendo Ventures, and Vanguard Venture Partners. Itasca focused on early-stage medical technologies that had not passed the proof-of-concept and prototype stages and aimed to nurture device

companies to viability. This incubator allowed us to invest in technology while still meeting Wall Street's financial expectations that often conflict with a focus on long-term development.

III. BUILD ON FDAMA TO BRING MORE BREAKTHROUGH THERAPIES TO PATIENTS

Today we face a golden opportunity to build on FDAMA's success and renew our commitment to the innovation and development of breakthrough technologies. And by "we" I specifically mean FDA and industry because through increased collaboration between the agency and companies, more breakthrough technologies will be developed and more patients will be helped. FDAMA created tools to foster collaboration, for example meetings between the agency and industry early in a device's development, which can be used to fine-tune the regulatory process for breakthrough technologies.

Indeed, FDAMA aimed to get devices, including breakthrough devices, to the public as soon as possible. FDAMA's expedited review provision identified four situations that triggered review priority including when devices represented breakthrough technologies. Key to FDAMA was increasing patient access to new technologies. The goal was to make review process more efficient and effective through streamlining and through meetings between the agency and premarket submitters that emphasized that only the least burdensome data to support an approval was required. These changes, although they put into law programs, had a smaller impact in providing patients with early access to breakthrough technologies.

Although these collaboration tools have been used to some benefit, I believe there are more tools that FDA and industry can use to further promote the development of safe and effective breakthrough therapies for critically ill patients. Specifically, a breakthrough device mechanism could be put into place, which—

- Requires FDA to designate breakthrough device status at an appropriate stage in the product's development—within 30 days of a submission requesting such a designation.
- Supports the development of protocols that include an "early look" at data to determine whether information exists to permit a safety and effectiveness determination and, thus, the earlier availability of a breakthrough device.
- Requires FDA to assign a team of reviewers with appropriate expertise to review a designated breakthrough device.
- Grants the device a preferred queue position both before and after submission of a PMA.
- Permits early and ongoing collaboration with the agency by providing for modular review, and requiring the applicant and FDA to communicate regularly after the premarket submission, to ensure the most detailed and efficient review.
- Requires that prior to a 90-day meeting, FDA provide a detailed, written review of any remaining deficiencies.
- States that the time to approval after the filing date is 120 days.

In essence, we would create a breakthrough device review process that offers early collaboration, access to expertise, and predictability. The process would be implemented by an FDA team that brings expertise to the review and has "ownership" of the breakthrough project. And through the collaboration encouraged by FDAMA, the breakthrough device process would result in high quality inputs in study design, data management, and review.

IV. CONCLUSION

I am confident that if we structure the review of breakthrough technologies, we will improve both the quality and timeliness of these premarket reviews and create incentives for breakthrough development. However, I remain concerned about the premarket review burdens that the FDA faces today. A breakthrough device mechanism can only function effectively if we supplement the number of reviewers and the expertise available to the agency. Indeed, the adequacy and stability of funding are critical. The task for the government and industry is to ensure that FDA is appropriately funded to face the challenges of the future. We have seen in the CDER experience that user fees have worked well. These fees assist the agency in providing the adequate number of reviewers with expertise to keep reviews timely. More importantly, they ensure the timely development and review of new products that provide a disproportionately positive impact on the public health.

Medtronic continues to fully support FDA's mission to improve the development of medical devices and help to ensure that safe and effective products are available to the American public. May we all continue to support this goal, especially in the area of breakthrough technologies.

Footnotes

[1] Linda Rochford and William Rudelius, *New Product Development Process; Stages and Successes in the Medical Products Industry,* Industrial Marketing Management, Jan. 1997.

[2] David B. Fleming and Thomas J. Sommer, Opinion, *Medical Devices Can't Keep Waiting,* The Boston Globe, Sept. 16, 1997, at D4.

[3] The Lewin Group, Inc., *Executive Summary, Report One: The State of the Industry,* March 24, 2000, at 3.

[4] Burton A. Weisbrod and Craig L. LaMay, *Mixed Signals: Public Policy and the Future of Health Care R&D,* Health Affairs, March/April 1999, at 112.

[5] Todd Nissen, *The Future of the Medical Device Industry,* Business Dateline; Corporate Report Minnesota, Dec. 1993, at 54 (citing a May 1993 report from the House Subcommittee on Oversight and Investigations which "noted that both industry representatives and FDA personnel discussed the possible threat to small medical device firms that couldn't afford to wait out the lengthy review process").

[6] *See, e.g.,* Manuel Schiffres and Jack A. Seamonds, *Is Red Tape Tying Up High Tech? Keeping the Genie in the Bottle,* U.S. News & World Report, April 21, 1986, at 50 (citing as an example "Pfizer's medical-devices group [which] screens research projects and focuses on new products that generally get hefty medicare reimbursements—the company may not develop some promising products 'simply because [Pfizer is] concerned that [it] won't be able to sell them in a market dominated by short-term cost-containment pressures'"); The Lewin Group, Inc., *Report One: Payment Issues for Medical Technology.*

[7] *See* Phil Galewitz, *Patients' Access to New Technology Is Being Increasingly Restricted by Insurers,* The Buffalo News, Nov. 2, 1998, at 3A ("Before providing coverage of new technology, health plans want proof that the products are cost-effective, work better than other technology, and improve or extend a patient's life.").

[8] The Lewin Group, Inc., *Executive Summary, Report One: The State of the Industry,* at 4; The Lewin Group, Inc., *Medicare Patient Access to Technology.*

[9] Chester A. Robinson, et al., *Encouraging Medical Device Innovation: Reimbursement Problems and New Policies,* Public Health Reports, Sept. 1, 1996, at 468 (noting that at that time approximately 94% of the 1200 devices being studied in FDA-approved clinical trials fell into the category of newer generations of proven technologies).

[10] The Lewin Group, Inc., *Executive Summary, Report One: The State of the Industry,* at 2.

[11] The Lewin Group, Inc., *Executive Summary, Report One: The State of the Industry,* at 4-5.

[12] Tom Abate, *Healing That Hurts; New Medical Devices Are Saving Lives But Killing Health Care Finances,* The San Francisco Chronicle, June 11, 1999, at B1.

[13] *See* Rochford and Rudelius, *New Product Development Process* (explaining that manufacturers of new products are more likely to use all the stages in the product development process, including a market study and test marketing, than manufacturers of devices which are product modifications).

NATIONAL FOOD PROCESSORS ASSOCIATION
June 12, 2001

The Honorable MICHAEL BILIRAKIS
Chairman
Subcommittee on Health
House of Representatives
Committee on Energy and Commerce
Washington, DC 20515

DEAR CHAIRMAN BILIRAKIS: The following are responses to follow-up questions with respect to the testimony I presented on behalf of the National Food Processors Association (NFPA) on implementation of the Food and Drug Administration Modernization Act (FDAMA) before the Subcommittee on Health on May 3, 2001.

NFPA is the voice of the $460 billion food processing industry on scientific and public policy issues involving food safety, nutrition, technical and regulatory matters and consumer affairs. NFPA's three scientific centers, its scientists and professional staff represent food industry interests on government and regulatory affairs and provide research, technical services, education, communications and crisis management support for the association's U.S. and international members. NFPA's members produce processed and packaged fruits and vegetables, meat and poultry, seafoods, drinks, and juices or provide supplies and services to food manufacturers.

Question 1. In FDAMA, the Congress created an alternative claim procedure wherein health and nutrient content claims could be based upon "authoritative statements" of the government. This is a different standard than "significant scientific agreement," which is required under the Nutrition Labeling and Education Act. Is it your view that the FDA has interpreted "authoritative statement" standard in such a way that it resembles the "significant scientific agreement" standard?

Response. It is NFPA's view that FDA clearly has tried to interpret the FDAMA provision in a manner that limits its application to those consensus-type statements that would survive the most restrictive reading of "significant scientific agreement." NFPA is on record challenging FDA's position.

FDA issued guidance in June 1998 (63 *FR* 32101, June 11, 1998), and interim final regulations banning nine specific FDAMA health claims, later that month (63 *FR* 34084, June 22, 1998), which documented the Agency's narrow reading of the "authoritative statement" provision of FDAMA, putting entirely in jeopardy the FDAMA premarket notification procedure. For example, FDA guidance takes the position that a statement of a federal agency does not qualify as "authoritative" unless it constitutes "the official policy" of the scientific body. Under FDA's interpretation, "subdivisions" of federal agencies apparently cannot issue "authoritative" statements, regardless of the scope of responsibility they have been delegated for public health matters (63 *FR* 34084 at 34085). Moreover, FDA makes clear that it does not intend to rely on the scope of authority delegated to a scientific body to determine whether its statements are authoritative, but rather to evaluate on a case-by-case basis the proceedings of scientific bodies to determine whether they are sufficiently deliberative to measure up to FDA's standards for approval of a health claim petition.

According to FDA, no statement will qualify as "authoritative" if it indicates "a relationship between a nutrient level and a disease or health-related condition is preliminary or inconclusive . . . (63 *FR* 34084 at 34086)." The Agency interprets FDAMA "to prohibit a health claim based on an authoritative statement when there is not significant scientific agreement that there is a relationship between the nutrient and the disease or health-related condition . . . (*Id.*)." This reflects FDA's basic view that FDAMA is a "surrogate" for, rather than an alternative to, the health claim petition process authorized by the Nutrition Labeling and Education Act of 1990. FDA's confined reading of FDAMA not only leaves little room for FDAMA health claims, but raises serious First Amendment concerns.

Question 2. FDAMA gave the FDA 540 days to review filed health claim petitions. Are you aware of any petitions which have exceeded this 540 day time limit?

Response. Since the enactment of FDAMA, we are not aware of any health claim petitions which have exceeded the 540-day time limit. Throughout the history of the health claim petition process, however, there are several petitions that have been withdrawn rather than pass through the gauntlet of FDA's health claim review time limitations. Typically, FDA scrutinizes health claim petitions at the beginning of the review process. The few health claim petitions that are filed, and survive the initial screening, allow for relatively easy docket management in FDA, enabling the Agency to reach closure by 540 days.

In addition, FDA has promulgated a rule (21 CFR § 101. 700)(4)) that requires the Agency to justify any delay in issuing a health claim final rule for a health claim petition if that final rule is not published within 540 days from the date of receipt of the petition. This date is earlier than the statutory deadline. On June 6, 2001 (66 *FR* 30311), FDA noted that the issuance of a final rule on the health claims, resulting from petitions, on plant stanol and sterol esters and coronary heart disease will be delayed until July 25, 2001. In this *Federal Register* document, FDA notes that the final rule will be issued within the statutory time frame.

Question 3. Has the FDA given any indication as to when it will revisit its advance notice of proposed rulemaking on irradiated products in order to finalize a rule which will provide consumers with better information about irradiated foods?

Response. On February 17, 1999, FDA published an advanced notice of proposed rulemaking (ANPR) calling for comments on labeling revisions for foods treated with ionizing radiation and suggestions on whether labeling requirements should expire. The ANPR highlighted the extensive public record FDA has already gathered on the subject and called for more information about consumer understanding of the irradiation process.

FDA's preliminary analysis of the comments it received suggests there is no consensus on what alternative language would be truthful and not misleading for disclosure of irradiation processing. The Agency believes that since these comments provide no clear direction for rulemaking, it has fulfilled its obligations under FDAMA's conference report that it provide an open public comment irradiation labeling issues.

In its recent response to the congressional request on irradiated labeling concerns raised in FDA's FY 2001 appropriation legislation FDA stated that it expected to receive a contractor's analysis of the comments on its ANPR by December 31, 2000. The Agency intends to: 1) obtain more information on consumer understanding of the existing label; and 2) attempt to develop a properly informative label that would not be perceived by consumers as a warning. If these projects are successful, FDA plans to develop a proposed rule during FY 2001 and publish a final rule by March 1, 2002.

On March 29, 2001, FDA indicated in a *Federal Register* notice that it plans to conduct six consumer focus groups on food irradiation labeling subjects in April and

May 2001, and sought comments on its request for approval by the Office of Management and Budget (OMB) for such research. NFPA understands that OMB has approved the research, and FDA now plans to conduct the series of focus groups on June 18, July 9, and July 11, 2001.

NFPA applauds the leadership this Committee has shown in oversight of the implementation of FDAMA and we appreciate this opportunity to provide the Committee with further information and comments. Please contact me if you need any additional information on the responses herein.

Sincerely yours,

RHONA S. APPLEBAUM, PH.D.
Executive Vice President, Scientific and Regulatory Affairs

GENERIC PHARMACEUTICAL ASSOCIATION
June 13, 2001

The Honorable MICHAEL BILIRAKIS
Chairman, Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

DEAR CHAIRMAN BILIRAKIS: Attached please find responses to the June 1, 2001 list of follow-up questions from the May 3, 2001 hearing on pediatric exclusivity you submitted to Dr. Carole Ben-Maimon, Chair of the Generic Pharmaceutical Association's Board of Directors. Please do not hesitate to contact me if you have any additional questions.

Thank you for your continued interest in this important matter.

Sincerely,

STEVE GIULI
Director of Government Affairs

Question 1: The FDA Report on Pediatric Exclusivity says that for children "the public health benefits have been extensive." Do you deny that this is the case?

Response 1. In order to evaluate the public health benefits of pediatric exclusivity there must be a clear understanding of what exactly the standard of measurement is. If the standard being employed is the number of studies that have been conducted prior to the pediatric exclusivity provision, compared to the number of studies that have been conducted after the provision became law, then there is no question that the pediatric exclusivity provision has achieved the desired objective. However, I do not believe that Congress intended merely to create an incentive for the performance of clinical studies. The intent, as I understand it, was to obtain valuable information and data that would have an impact on the treatment of childhood illnesses. Thus, the number of studies being performed is an inappropriate standard for measuring the provision's success. A more appropriate gauge would be to measure the quality of the data being generated and its value and application to those treating patients in the pediatric community. The Food and Drug Administration (FDA) is the only body possessing this information and is therefore uniquely suited to render a judgment on this basis. However, I have yet to see reports quantifying the impact and value of the data being obtained under the pediatric exclusivity provision. Only the FDA has access to this data. Clearly, without the necessary data it is inappropriate for me to offer an opinion on whether or not the public health benefits of the pediatric exclusivity provision, have "been extensive".

Question 2: The Tufts Center for the Study of Drug Development has found that without the pediatric exclusivity provision, the pediatric sales market itself would be insufficient to render the commitment of resources necessary to study drugs for use in children. Do you deny this?

Response 2. The short answer is, "No." In my May 3, 2001 testimony before the Health Subcommittee, I unequivocally expressed support on behalf of GPhA for the continued need for some kind of an incentive system to spur pharmaceutical research in the pediatric population. That view has not changed. GPhA fully supports research on therapies that are important for children. The concern I raised at the May 3 hearing, and one strongly held by GPhA, is that the magnitude and type of the current pediatric incentive cryout for careful Congressional review and continued scrutiny. The Generic Pharmaceutical Association strongly encourages the Commerce Committee to consider alternative incentives and programs that would achieve the desired result of pediatric research without harming other vulnerable sectors of the population by keeping drug prices high. And GPhA would welcome the opportunity to work with the Committee to develop such workable alternatives.

Question 3: The FDA has found that the pediatric exclusivity provision has increased the nation's pharmaceutical bill by one-half of one percent, while the Tufts Study found that the actual out-of-pocket expense for any senior citizen due to pediatric exclusivity is likely to be "minimal and temporary". Do you believe that a one-half of one percent increase is too much to pay for accurate dosing in children?

Response 3. The answer to this question requires a cost-benefit assessment. The answer clearly depends on the value of the information and the advances offered by the research. One area of concern about the cost of the existing system is that it places the entire burden of paying for that one half of one percent increase on the narrow section of patients who have to wait an additional six-months before the low-cost generic alternative for that particular brand drug to become available. The average retail price of a brand prescription costs 238% more than the average retail price of a generic prescription. For the senior citizen on a fixed income without prescription drug insurance, the added burden may well be "temporary" but it is hardly "minimal." The one half of one percent increase would, to that senior citizen, be a lot more affordable if it was being paid for by all of society instead of just a narrow and often vulnerable segment. We encourage Congress to look at alternate incentives that have less impact on people who are already struggling to pay for the high costs of their medications. We believe such alternatives exist, and we would welcome the opportunity to share our observations.

Question 4: In your testimony you note the fact that "pediatric clinical testing that does nothing more than assess children's reactions to the fifth or sixth generation 'me-too' drug makes no meaningful contribution to doctors' ability to treat the relevant disease". The decision about what does and does not make a meaningful contribution to pediatric health is up to FDA, not the drug manufacturer, however. If the FDA doesn't issue a Written Request, then there's no way that a drug can obtain pediatric exclusivity, correct?

Response 4. My understanding is that the FDA issues the written request, but in addition to that manufacturers can request a written request from FDA. Regardless of the process, FDA cannot differentiate between products within a therapeutic class. What benefit is there to society of rewarding, say, a fourth drug from a given therapeutic class when three drugs that are equally as effective have already received the pediatric exclusivity reward? This is a problem since FDA cannot reliably predict which companies marketing a specific drug within a class of drugs will perform pediatric studies. In addition, I am not aware that FDA has ever removed a product from its list. Thus, if three products with the same mechanism of action and for the same disease are studied the fourth product in the same category remains eligible for exclusivity even though the need may have drastically diminished.

As the process moves forward, Congress should also pay equal attention to the brand industry's campaign to minimize its obligations under the pediatric incentive program and convince FDA to narrow the scope of the Agency's study requests. Consider just these two examples.

In a letter to FDA dated April 3, 1998 Steven Spielberg, MD, John Siegfried, MD, and Marjorie Powell of PhRMA wrote "Studies can qualify for exclusivity even if they are unsuccessful and do not lead to new pediatric indications, dosing information, or formulations . . . [T]he study or studies need not lead to the filing of a supplemental drug approval application related to pediatric use to allow the applicable drug to qualify for the incentive."

On March 6 of this year, PhRMA's Alan Goldhammer, PhD, wrote a letter to FDA stating, " [I]f consensus between a sponsor and the Agency is reached that the diseases are the same in adults and children, then there should not be any requirement to conduct efficacy studies in children. Rather, information on pharmacokinetics to establish the appropriate dosing regimen, relevant formulations, and safety in children should be sufficient." If the requirements are so limited, why should the incentives be so large?

Contrary to these positions articulated by PhRMA, GPhA believes that the FDA should have the authority to require the timely addition of label revisions for pediatric uses and that brand companies should be required to conduct serious and original clinical studies in children in order to qualify for this large of an incentive. We urge Congress to consider these important issues in the reauthorization process.

Question 5: According to an January 2001 FDA report, between 1991 and 1996 (prior to pediatric exclusivity), only 11 pediatric studies were completed by the industry at the request of FDA. Since 1998 (after pediatric exclusivity), the industry has agreed to perform 411 pediatric studies. Don't you agree that significant progress is being made on behalf of children due to pediatric exclusivity?

Response 5. Again, it is GPhA's position that the quality of information and its relevance to the pediatric community, and not the number of studies, are the appropriate standards to use in determining the success of the pediatric exclusivity pro-

gram. An additional concern on this front is that an over-reliance on sheer numbers as an indicator of success can cloud the fact that clinical trials are a form of experimentation. With experimentation comes considerable risk. The deaths that resulted from the diprovan experience tragically illustrated just how severe the risk can be.

Question 6: The January 2001 FDA report estimated that lower hospitalization costs due to better pediatric dosing information can save up to $228 million per year for five diseases alone. Do you agree that by that measure alone the pediatric exclusivity provisions are having a positive impact?

Response 6. Reducing hospitalization costs was surely one of the objectives in creating a pediatric research incentive. Generating an annual $228 million savings over 5 years would, in turn, be a positive aspect of the pediatric incentive program. Allow me to again reiterate that GPhA strongly supports the continuation of some kind of incentive for pharmaceutical companies to conduct pediatric research. Having said that, GPhA believes that it is vitally important to accurately determine whether or not the current incentive is disproportionate to the cost. This concern is rooted in the belief there may be more cost efficient ways to create a pediatric incentive. Regrettably, a disproportionate financial incentive could encourage the exploitation of children. Combined, these two reasons make a powerful argument for considering alternatives to the current system that could better protect children with less of a cost to the public.

Question 7: You claim that pediatric exclusivity has been in place for four years, but that there is no well-defined system for measuring its success. However, in the five years before the provision was passed by the pharmaceutical industry conducted 11 pediatric studies at the request of the FDA, and since its passage they have agreed to conduct 411 pediatric studies. Isn't this proof enough for you that the provision is working?

Response 7. No. As discussed in earlier responses, GPhA believes the success of the provision should be measured by the quality and impact of the data it is generating and not just by the increase in the number of pediatric studies following the passage of the law in 1997.

Question 8: You mention in your testimony that the FDA claims the cost of the provision will amount to $695 million per year in higher costs of prescription drugs. That very same report says that better pediatric dosing could save $228 million in lower hospitalization and utilization costs for five pediatric diseases alone. It's entirely possible that this provision may save health care dollars, isn't that right?

Response 8. It is possible that this provision my save health care dollars but I would reiterate the points I made in my response to question 6.

Question 9: The generic industry will benefit by being able to label their drugs for pediatric indications when the brand name which conducted the pediatric studies comes off patent, correct?

Response 9. That is true if there is no patent and no exclusivity other than pediatric exclusivity associated with the drugs in question. One of the unintended repercussions of the pediatric exclusivity incentive is that as brand companies do pediatric studies, they may be seeking patents surrounding and protecting these concepts. The existence of a patent(s) that a generic company cannot use in its labeling raises an entirely different public health issue. Exclusivities may be prolonged beyond six-months as it is conceivable that additional patents could be issued.

MEDICAL DEVICE MANUFACTURERS ASSOCIATION
June 19, 2001

The Honorable MICHAEL BILIRAKIS
Chairman
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives
Washington, District of Columbia 20515-6115

DEAR CHAIRMAN BILIRAKIS: I have enclosed my responses to the questions you submitted to me for the record of your subcommittee's May 3 hearing on the implementation of the Food and Drug Administration Modernization Act of 1997.

Thank you for the opportunity to testify before the subcommittee and for your continued interest in the issues that affect the ability of the medical device industry to make new and advanced technologies available to patients who need them.

Very sincerely yours,

STEPHEN J. NORTHRUP
Executive Director

Attachment

Question 1. The FDA is on average reviewing 510(k) submissions in 77 days, and the premarket approval review time has been cut in half, though its still roughly twice what is required by law. Are the FDA's successes a result of FDAMA, FDA leadership, or both?

Response. Most of the credit for the reduction in medical device review times goes to the U.S. Congress for both their oversight of CDRH and their legislative efforts during FDAMA to ensure the necessary procedures took place to streamline the review process. The Center for Devices and Radiological Health (CDRH) and its own re-engineering efforts also deserve special recognition for reducing approval times by creating a more efficient and streamlined device review process.

Question 2. Have the collaboration measures contained within FDAMA improved the working relationship between manufacturers and the FDA? Has this come at the expense of patient safety?

Response. Overall the collaboration measures in FDAMA have improved the general communications between the medical device industry and the FDA. A survey conducted in 1999 by PricewaterhouseCoopers LLP and CONNECT, the University of California at San Diego's Technology and Entrepreneurship Program, found that communications between life sciences companies and the FDA have improved significantly since 1995, when the organization first began their bi-annual survey.

Unfortunately, the "formal collaborative meetings" between the Agency and industry as proscribed in the FDAMA provisions are underutilized, in large part because they are new and the industry has not developed a full body of positive experience to which others considering the merits of such meetings can refer. We nevertheless encourage the FDA to continue to implement these provisions, especially the collaborative meetings between the agency and industry to determine the type of evidence needed to support a PMA approval. It is beneficial for both industry and FDA to determine together the nature of the information needed for the industry to include in the device submission, as this will reduce the likelihood of arbitrary changes at a later date. This type of meeting helps to streamline the review process, thus ensuring that unnecessary regulatory requirements do not delay patients' access to new technologies.

There is no evidence to suggest that a more collaborative relationship between industry and the FDA has come at the expense of patient safety. The goal of FDAMA was to increase the regulatory efficiency of the FDA, not lower its standards.

Question 3. The FDA recently issued a Draft Guidance on the "least burdensome" provision contained within FDAMA. While I am concerned that it took FDA three and one-half years to develop this Guidance, could you explain for the Committee industry's general thoughts on this Guidance?

Response. As noted in my testimony, we are pleased that the FDA published this draft guidance on the "least burdensome" provisions of FDAMA in time for the May 3rd hearing. We believe this document captures the intent of FDAMA by defining "least burdensome" to mean an approach to addressing a premarket issue "that involves the most appropriate investment of time, effort, and resources on the part of the industry and FDA." When finalized, this guidance should have beneficial effects on the overall medical device review process.

Question 4. Even if the "least burdensome" Guidance is ideal from a public health and industry perspective, isn't it true that there will be little improvement in device reviews if the concept isn't thoroughly explained to the main line device reviewers?

Response. Everyone at FDA involved in the medical device approval process, from the division directors to branch chiefs to the front-line reviewers, must fully understand and adopt "least burdensome" principles in their day-to-day work to ensure its full implementation. We trust the agency will continue to train its reviewers and its advisory panels in the application of these concepts and principles. Training activities are crucial to promoting the greater consistency we seek in the FDA's review process.

Before the guidance can be put into effect, it must be published in final form. Therefore, it is important that CDRH expeditiously review and incorporate the appropriate comments and issue the final guidance in an accelerated fashion.

Question 5. Why did industry react so slowly to the third-party review process created within FDAMA? I understand that in the first 17 months after passage industry only used this process 54 times.

Response. It is true that this program has been used infrequently so far by the medical device industry, in large part because the FDA has streamlined its own review processes. However, we also believe industry underutilization of third-party review can be attributed in part to the manner in which FDA has implemented this program.

The FDA took more than three years to fully implement the third-party review provisions of FDAMA. The FDA's internal policy, as described in October 1998 and

November 1998 guidance documents, permitted third-party review of class II devices only if device-specific guidance or recognized consensus standards existed. In our opinion, limiting the use of the program through requiring the existence of guidance documents for the products in question was too restrictive and not in accordance with Congressional intent under FDAMA.

We argued to the FDA that products for which no guidance documents or consensus standards exist are exactly the types of products for which third-party review would be most attractive to manufacturers and most beneficial to the FDA. In January 2001, the FDA expanded this program to include any device regulated by CDRH that is not prohibited from third party review under FDAMA.

Question 6. Do you expect utilization of the third-party review to increase due to FDA's recent actions to expand the number of devices eligible for such review?

Response. According to the latest statistics released by the Agency, FDA has already received more third-party review applications in 2001 than were received in all of 2000. We believe this is directly related to the expansion of the program, and we look forward to its continued growth.

Question 7. Is there any evidence whatsoever that third-party review in any way compromises patient safety?

Response. According to FDAMA, the FDA accredits the independent organizations that are eligible to review the applications, and the FDA also has final authority whether to reject or accept the determination by the third party before the submission is cleared. The FDA would be in a better position to answer this question, but we are not aware of any situations in which a third party has recommended to the FDA that the agency clear an unsafe product. We also are unaware of any widespread compromising of patient safety in Europe, where non-governmental third parties conduct all premarket reviews of medical devices.

Question 8. Why did it take the FDA Centers so long to establish the dispute resolution procedure mandated by FDAMA? Do you have any idea when the Device Center's dispute resolution committee will hear its first dispute? Are companies willing to use such a procedure?

Response. As I noted in my written testimony, the FDA's first response to this provision of FDAMA was to publish a direct final rule on June 16, 1998. Under this rule, the FDA would have permitted drug and device manufacturers to request review of scientific controversies by an appropriate advisory committee. However, the FDA ended up withdrawing this rule after our industry and others complained that the rule was not consistent with the intent of FDAMA. As the FDA eventually acknowledged, the rule did not contain critical information, such as the process for selecting members of an advisory committee convened to resolve a dispute, the timeframes for conducting the reviews, the standards for granting or denying a review, and the weight to be given to advisory committee recommendations.

In the end, the FDA chose to allow each of its centers to develop a center-specific approach to implementing dispute resolution. For its part, the Center for Devices and Radiological Health (CDRH) has published a draft guidance document outlining how its dispute resolution process will work and has hired an ombudsman to oversee the workings of a Medical Devices Dispute Resolution Panel, which held its first organizational meeting in October 2000.

On June 4, 2001, the CDRH dispute resolution panel was scheduled to hear its first case, but the meeting was indefinitely postponed. As I understand it, the meeting was postponed because the FDA and the company had major disagreements about materials that were distributed to panel members shortly before the meeting.

I believe that companies are willing to use this procedure if they believe they will be guaranteed a fair hearing. With respect to the postponed June 4 meeting, the company involved may have been concerned that the materials the panel members received from the FDA would have biased the panel against the company and its case.

For the most part, companies usually try to resolve disputes at a lower level by going through normal administrative channels or the recently established CDRH ombudsman's office. Nevertheless, it is important for companies to have a mechanism like this dispute resolution panel available, provided that the panel and its decisions are independent and free of any agency bias. We will continue to monitor the implementation of this FDAMA provisions and will report our findings to you.

Question 9. Is the industry availing itself of the collaborative meetings, whether on a pre-IDE or pre-PMA basis, which are provided for in FDAMA? Have these meetings proved beneficial?

Response. Overall, industry has found the collaborative meetings mandated by FDAMA to be productive and useful, although as I mentioned earlier, they have been underutilized to date in our opinion. Most of the meetings in which the FDA and industry have participated have resulted in agreements, although some of our

members report that the FDA for some reason has been reluctant to engage in 180-day meetings on major premarket approval application (PMA) amendments.

QUESTIONS FROM ANNA ESHOO

Question 1. Despite extensive scientific evidence demonstrating serious risks associated with reprocessing of single-use medical devices—including several studies conducted by the Agency itself—FDA has failed to meaningfully enforce key patient safety provisions of the Food, Drug and Cosmetic Act. It took substantial Congressional and public pressure to force FDA to finally publish enforcement guidance on regulation of this potentially dangerous practice. Yet, I remain concerned that this guidance, while a step in the right direction, continues to permit the use of many unsafe reprocessed devices on American patients.

Mr. Northrup, I know your organization has been actively involved in working with FDA to develop a strategy to regulate the reprocessing of single use medical devices. Would you comment on FDA's progress in implementing its strategy to regulate this practice?

Response. On August 14, 2000, the FDA released a guidance document, titled "Enforcement Priorities for Single Use Devices Reprocessed by Third Parties and Hospitals." The guidance document, if properly implemented, will require reprocessors of some single use devices to fulfill substantially the same pre-market submission requirements as original manufacturers of single use devices. While the guidance document represents a step forward in the enforcement of the Food, Drug, and Cosmetic Act ("FDC Act") on some reprocessors, it also presents new risks to patient health and perpetuates the regulatory inequity between reprocessors and original manufacturers by exempting reprocessors from fulfilling premarket requirements for certain devices.

According to the guidance document, FDA intends to subject reprocessed single use devices to pre-market submission requirements based on their original device classification (Class I, II, or III). Under this classification scheme, FDA and its expert panels have "exempted" certain new devices from 510(k) and PMA requirements because these requirements were not deemed necessary to ensure the safety of the devices for one use. Instead, the FDA intends to extend blindly these premarket exemptions to reprocessed devices even though the original expert panels *never* considered the reuse of these devices, and even though these exemptions will not consider the new questions of safety and effectiveness raised by reprocessing devices designed for single use only.

The FDA broadly extends these pre-market exemptions to hundreds of reprocessed single use devices while at the same time admitting that many of these devices, although exempt (e.g., non-electric biopsy forceps), may present a greater risk to patients when reprocessed. The FDA's answer to this dilemma is to examine at some point in the future "high-risk" devices such as non-electric biopsy forceps on a case-by-case basis to determine whether the exemption should still apply. Thus, the FDA inappropriately presumes the safety and effectiveness of these reprocessed single use devices.

Moreover, the FDA shifts the burden to original manufacturers who design, develop and manufacture these devices to demonstrate the need to revoke exemptions on a case-by-case basis rather than requiring reprocessors to meet the burden for obtaining an exemption or filing a 510(k). This position is inconsistent with the FDC Act, the FDA's regulations, sound policy, and patient safety. The burden of affirmatively demonstrating safety should be placed on the party that always has the burden under the FDC Act: the party that wishes to market the device. Patient safety and consistent, sound policy, therefore, require that reprocessors meet the burden of demonstrating safety and effectiveness of a reprocessed single use device in a 510(k) or a petition for exemption.

Question 2. Can you give me a specific example of a product where you feel that FDA has failed to take appropriate steps to ensure patient safety? What can FDA do in this instance to ensure the reuse of this product does not pose a public health risk?

Response. A specific example of a product for which the FDA has failed to take appropriate steps to ensure patient safety is reprocessed single-use non-electric biopsy forceps. These devices are currently exempt under the new regulatory scheme, and reprocessors are not required to demonstrate their safety and effectiveness through the 510(k) clearance process prior to placing these devices on the market.

Non-electric biopsy forceps are used to obtain deep patient tissue samples in various gastroenterology procedures in order to diagnose the presence of such diseases as colon cancer, Crohn's, ulcerative colitis or Barrett's esophagus. Single-use biopsy forceps break the mucosal barrier and come in contact with the blood stream and

are difficult, if not impossible, to thoroughly clean or adequately sterilize for safe reuse without adversely affecting the structural integrity of the device. The very design of non-electric biopsy forceps impedes adequate cleaning and sterilization after use. In addition, the harsh conditions of reprocessing diminish the performance and structural integrity of the device.

Single-use non-electric biopsy forceps are comprised of two long, thin steel wires that are surrounded, at the distal end, by a lubricious-coated plastic sheath. The wires and inner sheath are located inside a tightly wound metal coil which is then encased in an outer polymer sheath up to 240 cm long with an outer diameter as small as 2.2 mm. These long, narrow lumens are one of the hallmark features that make this device difficult to reprocess. The coil that surrounds the inner plastic sheath creates many difficult-to-access interstices in which debris accumulates during use.

The jaw assembly of the device often includes a needle for anchoring the biopsy into the mucosa. The needle is also used to stack biopsy samples for detainment in the jaw assembly. The needle directly penetrates the mucosal layer of the GI tract and should be considered in the same manner as all medical device "sharps" classification.

Because biopsy forceps break the mucosal barrier and come in contact with the blood stream, sterility is critical. However, the results of several studies have consistently demonstrated that a significant number of reprocessed single use biopsy forceps contain residual debris and fall below the sterility assurance level established by the FDA as appropriate for most medical devices. Specifically, in Boston Scientific Corporation-sponsored studies performed by independent laboratories, more than 64 percent of reprocessed devices randomly selected from hospital shelves failed the sterility tests and over 94 percent tested positive for the presence of residual tissue.[1] Furthermore, in studies conducted by the FDA's Office of Science and Technology using three types of single-use gastrointestinal biopsy forceps, researchers found that, in cleaning the devices with a sequence of bleach, ultrasonic bath with detergent and enzyme, and water rinse, residual water remained in the devices. This inability to dry the device lumen decreases the effectiveness of sterilization.[2] Thus, even when debris can be removed from these devices, the existence of residual water compromises the ability to sterilize them.

In FDA's initial draft guidance to regulate the practice of reprocessing, FDA listed biopsy forceps on its list of products that are frequently reprocessed. Interestingly, due to concerns regarding the sterility and efficacy of the product after reprocessing, the agency classified reprocessed biopsy forceps as a Class III "high-risk" product, a decision which, if implemented, would have subjected the reprocessed device to the agency's most stringent pre- and post-market regulatory controls.

In short, reprocessing of biopsy forceps designed and labeled for single use, with its potential for residual debris, non-sterility, and compromised functionality, presents an increased risk to patients. This risk necessitates rigorous review by the FDA via 510(k) clearance to ensure that these single-use devices are in fact safe and effective for reuse after reprocessing. The FDA must require reprocessors to provide data demonstrating the efficacy of cleaning and sterilization of biopsy forceps and verify their functionality before allowing these devices back into the marketplace. The FDA, therefore, must immediately revise its regulation that exempts all non-electric biopsy forceps from pre-market notification procedures and require 510(k) clearance for these devices, prior to these reprocessed devices being placed on the market and used on a patient.

Question 3. Mr. Northrup, you testified to the importance of "fair, predictable, and consistent regulatory actions" during the FDA approval process. When we wrote FDAMA, we included a provision mandating that the evidence required for FDA approval be the "least burdensome" needed to meet safety and effectiveness standards. In your opinion, has the FDA implemented this "least burdensome" requirement in a timely manner?

Response. In my opinion, the Agency has not implemented the "least burdensome" requirement in a timely manner. It took the FDA until May 1, 2001, to release the draft guidance document on this subject. This delay of more than three years since the passage of FDAMA is a critical shortcoming of the agency's implementation efforts, as these provisions capture best the true spirit of FDAMA—ensuring that unnecessary regulatory requirements do not delay patients' access to new technologies.

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[1] *See* BSC Citizen Petition, at 6-8 (FDA Docket No. 00P-1535) (Sept. 20, 2000).

[2] *See* CDRH, "Reprocessing Single Use Biopsy Forceps for Reuse," Abstract for the 2000 FDA Science Forum from OST.

Upon review of the recent draft guidance document on "least burdensome", we believe it upholds the basic principles outlined in the FDAMA provisions, and we will be recommending to the FDA that they accelerate the finalization of this guidance.

CHILDREN'S MERCY HOSPITALS & CLINICS
DIVISION OF PEDIATRIC PHARMACOLOGY AND MEDICAL TOXICOLOGY
7 June 2001

Hon. MICHAEL BILIRAKIS
Chairman, Subcommittee on Health
U.S. House of Representatives
Committee on Energy and Commerce
Washington, D.C. 20515-6115

DEAR CONGRESSMAN BILIRAKIS: Thank you for your letter of 01 June 2001 concerning my testimony of May 3, 2001 to the Subcommittee on Health regarding the Food and Drug Modernization Act. It was truly a distinct honor and privilege for me to have been invited to share my perspectives and recommendations with the Congress pertaining to the pediatric provisions of this Act. I also sincerely appreciated the hospitality that was extended to me by you, the members of the Subcommittee on Health and the Committee staff as it made my experience both enjoyable and memorable.

Enclosed with your letter was a list of three questions for me to consider and provide responses to. It is with great pleasure that I do so at this time. As per the instructions contained in your letter, each of the three questions and my responses to them are provided in the enclosed document.

Again, thanks so much for inviting me to participate in the hearing on FDAMA and by doing so, affording me an opportunity to serve. If I can ever be of assistance to you and/or the other members of the Subcommittee on Health, please do not hesitate to call upon me.

Sincerely,

GREGORY L. KEARNS, Pharm.D., FCP
Chief, Division of Pediatric Pharmacology and Medical Toxicology

Encl.

Question 1: In your testimony, you claim that "in four short years, pediatric exclusivity has done more to improve the health and welfare of children than any other pediatric therapeutic initiative in the history of our country". Could you explain the hazards of not re-authorizing this legislation?

Response: Failure to reauthorize the pediatric provisions of FDAMA would dramatically reduce the number and scope of pediatric clinical drug trials of marketed prescription drug products and thus, prevent the generation of objective, scientifically-based information required (and requested by physicians) to insure the safety and efficacy of drug treatment in neonates, infants and children. For example, since FDAMA was enacted, a total of 154 different therapeutic drug moieties have been the subject of 409 carefully controlled clinical investigations performed consequent to 189 formal written requests issued by FDA. These clinical investigations, all of which were conducted with the rigor that accompanies FDA oversight, have involved well over 50,000 pediatric patients spanning in age from birth through adolescence with a variety of common (and potentially serious) medical conditions (e.g., asthma, hypertension, diabetes, pain, anxiety, sepsis) seen in pediatric and adult patients alike. Thirty three of these drug products studied in pediatric patients under the provisions of FDAMA have been granted extended marketing exclusivity; 17 of which have produced significant changes in product labeling (i.e., the prescribing information made available to physicians) that have the potential to prove both the safety and efficacy of these drugs in infants, children and adolescents. In stark contrast, *only 11 drugs* were formally (i.e., under the aegis of the FDA) studied in pediatric patients in the 10 year period preceding the enactment of FDAMA. In conclusion, failure to renew FDAMA and its pediatric provisions would return infants and children to the status of "therapeutic orphans" and thus, deny them the same rights to drug treatments which are proven to be safe and effective as we afford adults through the formal process of drug development mandated by the FDA.

Question 2: Is it your belief that FDA's Written Requests for pediatric studies can be overly burdensome and impractical at times, resulting in manufacturers deciding not to conduct pediatric studies?

Response: In some instances, this has indeed been the case; the reasons for which are multifactorial. Some of these reasons are as follows:

- The process of consultation, collaboration and negotiation between a pharmaceutical sponsor and the FDA that ultimately results in the issuance of a Written Request may take anywhere from 6 to 18 months. For drug products where patent life is limited with respect to when the Written Request is issued, the sponsor may not have sufficient time to conduct the required pediatric studies in a manner that is safe (for the subjects) and ethically defensible.
- The FDA may require the study of a drug in a specific subgroup of pediatric patients (e.g., neonates and infants) despite the fact that the drug product being considered for study under a Written Request may not have substantial therapeutic use in these particular patient groups. This markedly increases the time required to complete a pediatric clinical study program if the FDA mandates that for any drug that is the subject of a Written Requests, the entire pediatric age range (i.e., birth through adolescence) must be included in the clinical trials.
- The decision by the FDA whether or not to include formal studies to prove drug efficacy (e.g., phase III clinical trials) has been liberally interpreted by the Agency in several instances by the Agency despite the fact that a pharmaceutical company may not be seeking an indication-based label claim (i.e., a recommendation for treatment of a specific pediatric disease/condition) as part of a pediatric study program conducted under a formal Written Request. In many instances, "bridging studies" to determine age-specific drug dose, provide demonstration of drug effect and provide limited safety/tolerability information are more than sufficient to produce significant improvements in product labeling and thereby, enhance the safe and effective use of drugs by pediatric practitioners. These studies can generally be accomplished without compromise in relatively small numbers of well selected patients and in a reasonable time frame (e.g., 12-18 months) as opposed to the 2 to 3 years that generally is required to conduct clinical trials that are sufficiently designed and powered to prove drug efficacy. To insure the treatment benefits of FDAMA for children and that no more pediatric patients than is absolutely necessary are subjected to the risks and rigor associated with any clinical trial, the FDA must only require pharmaceutical companies to obtain information that is required to fill the information gaps necessary to improve pediatric drug use. The Agency must not be in a position to complicate the process of pediatric clinical drug trials by asking pharmaceutical companies and in turn, clinical investigators and the parents/guardians of the research subjects (i.e., patients) to provide data that may well be "interesting" but because of study limitations, are inconclusive. Many of the aforementioned problems/challenges during this first chapter of FDAMA can be minimized or prevented by creation of an Office of Pediatric Therapeutics within FDA and insuring that this new Office is appropriately funded and staffed so that it might truly serve as a focal point of expertise and operational capability for all pediatric clinical trials being considered and/or reviewed by the Agency.

Question 3: In its report to Congress, the FDA noted that the pediatric exclusivity provision does not create adequate incentives for conducting studies in newborn infants. Why do you believe neonates are not being studied as much as other pediatric age groups? What can be done to ensure that neonates are studied in the future?

Responses: Neonates (i.e., infants less than one month of life) represent a small segment of the entire pediatric population and account for a relatively small proportion of pediatric drug use in general. Despite this fact, approximately 20% of all pediatric clinical drug trials conducted as part of a Written Request issued by FDA in the first four years of FDAMA involved neonates. As well, with the possible exception of drugs used to treat infections (e.g., antibiotics, antifungal agents, antiviral agents), the 10 most common conditions that afflict neonates are managed with fewer than 25 different therapeutic drugs. Thus, relative to older infants and children, the therapeutic "need" for drug products in the neonatal population is focused and somewhat limited in scope. Hence, I know of no evidence suggesting that neonates are routinely being excluded from participation in clinical drug trials

Clearly, the "need" to include neonates in a clinical trial should be driven by a demonstrated therapeutic need for a given drug product in this particular pediatric sub-population. It should not be driven by some mandate to include them simply because they are part of the pediatric population when patterns of drug use and/or clinical standards of care do not support substantial use of a given drug in neonates. When there is a therapeutic need for a drug in the neonatal population, it is imperative that these patients be included in clinical trials that are appropriately designed for neonates, taking into consideration that these subjects will be sick patients that have a host of physiologic and disease-associated constraints that influence what can and should be done. Appropriate scientific oversight afforded by effec-

tive collaboration between pharmaceutical companies, FDA and academic experts will insure that neonatal studies are done only when therapeutically, necessary and in a manner that is safe, effective and scientifically rigorous so as to produce the kind of information that clinicians who care for sick newborn infants demand and deserve.

ELI LILLY AND COMPANY
June 7, 2001

MICHAEL BILIRAKIS
Chairman—Subcommittee on Health
Committee on Commerce and Energy
U.S. House of Representatives
Washington, DC 20515-6115

DEAR CHAIRMAN BILIRAKIS: On behalf of the Pharmaceutical Research and Manufacturers Association (PhRMA) of America, I express our appreciation for the opportunity to share our perspectives on the Food and Drug Modernization Act (FDAMA) at the May 3rd hearing of the Subcommittee on Health.

In response to your correspondence of June 1, 2001, including questions from your members, the attached material represents PhRMAs position on those matters in the format which you stipulated, and is submitted within the June 10, 2001 deadline which you requested.

Please contact Drs. Bert Spilker or Alan Goldhammer at PhRMA or me directly should there be any questions about this or other material, or if we can be of any other service.

Sincerely,

TINOTHY R. FRANSON, MD
Vice President, Clinical Research
and Regulatory Affairs-U.S.

Enc.

Question #1: Some today have claimed either in their written or oral testimony that by allowing drugs to be introduced in the U.S. before the rest of the world,, somehow the American people are being used as "guinea pigs." I believe it's better to have drugs introduced in the U.S. first. Do you agree?

Response to #1: PhRMA strongly agrees that American patients benefit from first global approvals in the United States. Most of the research on new drugs is conducted in the United States and in the past, notably pre-PDUFA American patients have had to wait, sometimes for significantly long periods of time before they could benefit from these new medicines. New drugs provide incremental or breakthrough advantages to patients in need, and it is clearly in the interest of public health to expedite such access. The volume and quality of information provided by NDA (new drug application) sponsors to FDA, and the degree/quality of scrutiny provided by FDA for such submissions continue to be the global standard. Over the past decade, FDA has consistently added new safety and efficacy requirements for drug researchers to study during the development process indicating an enhancement of the regulatory process rather than any diminution as their critics might have you believe. Finally, all newly approved drugs have a justification summary (termed "Integrated Summary of Benefits and Risks") that summarizes the attributes of new products to make assessments transparent.

Question #2: Have the reforms contained within FDAMA led to better collaboration between the FDA and the regulated industry?

Response to #2: FDAMA has remarkably improved multiple aspects of drug development processes, including roles and responsibilities for sponsors and FDA. As such, the regulated industry and FDA have worked toward improved, clear, commonly defined (improved) standards that the respective parties execute independently. Therefore while FDA and industry representatives collaborated with Congressional staff in 1996-97 to refine standards, resulting in FDAMA, and while industry and FDA may collaboratively plan studies to ensure expectations of all stakeholders, actual development work and reviews are pursued independently to assure process integrity.

Question #3: Since FDAMA was enacted, there have been 108 requests for designation as a "fast track" drug, and 69 of these requests were granted. Has this procedure led to quicker approval for drugs intended to treat serious or life-threatening diseases?

Response to #3: While we have observed that there have been some rapid approvals of oncology and AIDS medications, PhRMA is not in a position to generalize how

effective this provision has been. We suggest that the Committee may want to contact the FDA to obtain the actual approval data.

Question #4: Part 1—How has the pediatric exclusivity provision affected drug companies internal decisions about whether to test new molecular entities in pediatric populations?

Response to #4: Part 1—There is no question that this provision has had aprofound positive effect on the pharmaceutical industry. Many of the studies required new formulation development to cover younger age ranges of patients, as well as the development of novel clinical trial designs and tools to evaluate safety and/or efficacy. Requests have covered drugs in a wide range of therapeutic areas from common problems such as treatment of fever and simple skin infections, to cardiac disease, endocrine problems, gastrointestinal disorders, serious infections including HIV, seizure and other neurologic disorders, and management of pain. Studies have included pediatric patients across all ages. The range of conditions addressed, the variety of drugs being studied, and the nature of the scientific data requested all suggest that FDAMA is successfully addressing unmet therapeutic needs in children. No other approach, legislative or regulatory, has had such a profound impact on the evaluation of medicines in children.

Question #4: Part 2—Has it elevated pediatric drug development in the eyes of Research and Development directors?

Response to #4: Part 2—Yes it has. It is critically important to remember that research resources are finite. Pediatric studies are always in competition with studies of important new medicines for large numbers of adult patients. By establishing a financial incentive, Section 111 of FDAMA raises the priority for pediatric studies. By focusing on the needs of children, and recognizing fundamental impediments to pediatric drug development, the legislation is accomplishing the goals set forth by Congress.

QUESTION FROM BART STUPAK:

Dr. Franson, in your testimony, you mentioned that post-market surveillance is mandatory. It is actually voluntary. Would you support mandatory postmarket surveillance?

Response to Bart Stupak:

The testimony comment was to illustrate that post-market surveillance "activities" regarding drug safety are mandatory—that is, any sponsor holding an approved NDA is required by FDA regulations to capture and report any and all post-approval adverse events to FDA in timely fashion. 21 CFR Part 314.80 outlines the specific regulatory requirements that pharmaceutical companies are required to follow. Companies must report any serious or unexpected adverse event to the FDA within 15 days of receiving such information. Companies also follow up these reports to better understand what has occurred with the drug. There is also a requirement to submit, at quarterly intervals during the first three years the product is on the market and annually thereafter, any adverse drug experience that doesn't fall into the serious or unexpected category. Furthermore, PhRMA companies devote extensive professional staff to not only adverse event collection—but also event trend analysis and proactive, independent safety labeling changes.

There are also selected circumstances in which various extents of post-market surveillance programs (from simple registries to restricted access) may be useful, depending on the benefit/risk characteristics of a product. It would not be advisable to mandate post-introduction surveillance studies for all—or most—new products without a well-defined plan, expected yield and patient cost-benefit projections supportive of such interventions.

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
June 29, 2001

The Honorable MICHAEL BILIRAKIS
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

DEAR MR. CHAIRMAN: Thank you for your continued interest in the Food and Drug Administration's (FDA or Agency) successful implementation of the Food and Drug Administration Modernization Act (FDAMA). This letter is in response to the Com-

mittee's additional questions raised in your letter of June 1, 2001. Thank you for making this a part of the public record. The response to question 24 contains information not releasable to the public and we ask that the Committee not make public or publish that information.

Your questions will be restated, followed by our response.

Question 1. What impact have user fees had on the information technology systems within FDA? Are we closer to a paperless system of review?

Response. As you know, FDA collects user fees for a limited number of product review activities primarily drug and biologics review and color additive petitions. FDA's Center for Drug Evaluation and Review (CDER) has been able to improve its infrastructure to accept more electronic applications. Following is a summary of the initiatives that CDER has undertaken to be able to move to a paperless system.

- Expanded the Electronic Document Room (EDR) to manage the receipt and handling of full electronic new drug applications. Around 75 percent of original new drug applications received in CDER now include sections that conform to the electronic submission guidance. In Fiscal Year (FY) 2000, CDER received over 500 electronic submissions, including full new drug applications, supplemental new drug applications (NDA), and amendments. There has been a 50 percent decrease in the average number of paper volumes per NDA submission since the start of electronic submissions in 1997.
- Accepting expedited postmarketing adverse event reports without attachments in electronic format. A number of sponsors have successfully sent reports electronically that have been directly transferred to a database. The Agency is also preparing regulations to require all adverse event reports from industry to be submitted electronically.
- Implemented the Division Files System, which provides document management, tracking, archiving, electronic signature, and search capabilities for internally generated review documents.
- Developing guidance for submission of postmarketing expedited safety reports, drug registration and listing information, investigational new drug (IND) applications; NDA annual reports, drug master files (DMF) in electronic format.
- Finalizing a proposed rule that would require NDAs to submit final printed labeling content electronically to the Agency for review. Interested parties will have an opportunity to comment.

Since 1997 user fees have significantly impacted the Information Technology (IT) systems in FDA's Center for Biologics Evaluation and Review (CBER). User fee support has made it possible for CBER to have the technology infrastructure in place to store, retrieve and review electronic documents. Before the IT investments of the second reauthorization of the Prescription Drug User Fee Act (PDUFA), CBER's ability to receive and use electronic submission material was non-existent. CBER's electronic mail (e-mail) system did not support attachments and staffs found themselves limited by antiquated and sometimes obsolete technology. Most CBER computers could not support a business software suite, Internet browser, or other common place business products.

The FDAMA and PDUFA reauthorization mandates the creation of a paperless submission and review environment within FDA by the year 2002. In accordance with the Paperwork Reduction Act (PRA), Information Technology Management Reform Act (ITMRA), Electronic Freedom of Information Act (E-FOIA), and National Performance Review (NPR), FDA has created strategic plans and programs to reach the intended goals. Following is a summary of the CBER projects initiated to meet the goal of a paperless environment in 2002.

- An EDR has been designed and built to support the required performance goals and international standards, enabling a paperless submission and review environment. This electronic repository was constructed using the requirements of CBER's Managed Review process, which defines a systematic approach to submission review. The EDR provides an electronic receipt point for volumes of electronic submission material, the capability to securely view regulatory submissions, the ability to communicate electronically with Industry, and the ability to manage electronic records and archiving of regulatory submissions.
- To meet the electronic submission review timetables and milestones, a network, software and computer infrastructure was constructed. This infrastructure is standardized across the Agency and has increased the data transfer speed from 1.45mbs to 100mbs. In addition, redundancy has been added to the network to ensure reliability.
- CBER issued Biologics License Application (BLA) regulations and guidance to industry through the Federal Register ("Biological Products Regulated Under Section 351 of the Public Health Service Act: Implementation of the Biologics Li-

cense; Elimination of the Establishment License and Product License," 10/20/99) Existing Product License Applications (PLA) and Establishment License Applications (ELA) or their Supplements were merged into a single BLA as a consequence of the final rule since it provided that applicants who already had an approved ELA and PLA for a product would not be required to make additional submissions to comply with the new requirements.

- A new Regulatory Management System to track and report on BLA status was developed. This system was designed to satisfy new business rules and approximately 900 requirements associated with BLAs and to merge pre-licensing and licensing components of an older legacy system. BLAs replace ELAs and PLAs that have been submitted to CBER separately in the past.

Today, CBER's entire workflow process has changed with the technological enhancements made possible by user fees. CBER now uses a robust e-mail system as a part of its standard software suite and has the computer and network infrastructure to support a host of new systems developed specifically to manage submission material and help CBER meet its goal of a paperless review environment in 2002. User fees made it possible for FDA to develop guidance documents and databases to track the status of submission reviews. As a result, the review process is well defined, accountable, and scientifically sound. Since 1994, FDA has submitted an annual Performance and Financial report to Congress on progress in meeting performance goals and the use of fees. (See http://www.fda.gov/oc/pdufa/reports.html.)

For FDA's Center for Food Safety and Applied Nutrition (CFSAN), the only user fees authorized to be collected involve its Color Certification Program. The fees are collected to certify color batches and enable CFSAN to keep the IT systems for the Color Certification Program current and state-of-the-art. The Color Certification Program has developed a database system that allows Agency analysts to enter analyses of color batches into the Color Certification Tracking System (CCTS) as they are completed. FDA's CCTS provides industry with real-time information about their color samples as they are being processed. The CCTS also provides the industry with timely final certification data that allows them to sell a color additive days before they receive the hard-copy certificate. CFSAN is working to develop in 2002 an automated system that will allow industry to submit electronically its requests for certification of color batches.

The medical device program does not have user fees, however, the Agency encourages device manufacturers to provide device submissions electronically. The Center for Devices and Radiological Health (CDRH) received 113 electronic submissions in FY 2000. Instructions for submitting electronic submissions can be found on FDA's home page at the address http://www.fda.gov/cdrh/elecsub.html.

The CDRH does, however, under its radiological health statutory charge, collect user fees as part of the Mammography Quality Standards Act (MQSA) of 1992. The collection of MQSA user fees has enabled the program to develop and maintain specialized databases (Mammography Program Reporting Information System [MPRIS]) that track inspections, inspection results, and facility billing for the approximately 9,700 facilities that are inspected annually. Using the MPRIS database, findings and trends can be analyzed and used for program management. User fees allowed the division to procure the services of an IT contractor to assist in the design, development, and support of the system. Thus, FDA was able to meet very tight statutory deadlines, without utilizing already overburdened CDRH resources. A laptop and printer are used on site by each inspector to record inspection data, upload to headquarters, and leave a post inspection report with the facility.

Question 2. In January of this year, the FDA issued a glowing report in favor of reauthorizing the pediatric exclusivity provision. In the report, FDA claimed that "the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information than any other regulatory or legislative process to date." Why has this provision proved so successful when others have failed?

Response. We believe this provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date because the legislation provides financial incentives to the sponsors. Even though this provision has been successful, there are gaps in the success story we would like to bring to your attention as follows:

- Exclusivity is granted for submitting pediatric studies not for label changes incorporating pediatric information. Thus, there have been some delays in getting information in drug labels, particularly adverse information.
- There are drugs with no remaining patent or exclusivity that are not eligible for the financial incentive that makes it more difficult to obtain pediatric studies.
- Studies in some of the youngest children, particularly newborns and young infants, are often delayed due to scientific and ethical reasons. Obtaining these studies is difficult, as there is no sufficient, additional financial incentive.

Question 3. As of today, 28 drugs have received pediatric exclusivity, and 18 of these have had pediatric label changes. Out of the ten, which have not had label changes, is it expected that many if not all of these will eventually have label changes?

Response. We believe that eventually most of the drugs that have been granted exclusivity will have label changes. Since the grant of pediatric exclusivity is not tied to a requirement that label changes be made, there may be cases in which information will not make it into the label. In FDA's experience, delays in obtaining label changes are more likely when the study has produced negative information about the drug's use in children. Delays in getting this kind of information into the drug label may jeopardize children's health.'

Question 4. In its January 2001 Report the FDA claimed that the pediatric exclusivity provision added one-half of one percent to the national pharmaceutical bill. The FDA also found that the provision could lead to substantial health care savings due to lower hospitalization rates for children. Is it possible that the pediatric exclusivity provision may in fact save health care dollars, like the Tufts Center for the Study of Drug Development suggested?

Response. We believe that the benefits of the pediatric provision include savings of health care dollars due to lower hospitalization rates. The lower hospitalization rates can be predicted from the significant dosing and safety information already obtained and incorporated in the first 18 products labeled with pediatric use information. For example, the information showing proper dosing for gabapentin for children three years to 12 years old should result in fewer seizures and the need for fewer additional medications. The appropriate dosing of fluvoxamine will lead to fewer medication changes and potentially the prevention of suicide attempts in adolescents because of poorly controlled obsessive compulsive disorder. For etodolac, patients with juvenile rheumatoid arthritis will experience better relief of their pain and improved mobility now that we know children need higher doses than adults do. While we do not have sufficient information to quantify these benefits, it is theoretically possible that the savings from these benefits are greater than the costs to consumers, pharmacists, and generic drug companies.

Question 5. The 9th Circuit Court of Appeals recently held pharmacy compounding provisions of FDAMA unconstitutional due to their restrictions on commercial speech. Will the FDA challenge this decision all the way to the Supreme Court? If not, will it enforce the FDAMA provisions outside of the 9th Circuit?

Response. As you know, on February 6, 2001, the U.S. Court of Appeals for the Ninth Circuit issued a ruling. They affirmed in part and reversed in part a decision of the U.S. District Court for the District of Nevada involving a challenge to the constitutionality of two speech-related restrictions in section 503A of the Federal Food, Drug and Cosmetic (FD&C) Act (pharmacy compounding).

Section 503A, which was enacted as part of FDAMA, exempts compounded drugs from the FD&C Act's new drug approval, adequate directions for use, and good manufacturing practice requirements if specified conditions are met. The provisions at issue provide that in order to qualify for the exemption, the compounded drug may not be based on a solicited prescription, section 503A(a), and the pharmacy, pharmacist, or physician may not advertise or promote the compounding of a particular drug, class of drug, or drug type, section 503A(c).

The enforcement of these two conditions has been enjoined since December 18, 1998, although the rest of section 503A remained in effect. The appellate court agreed that section 503A's restrictions on commercial speech violate the First Amendment. The appellate court, however, concluded that the speech restrictions in section 503A(a) and section 503A(c) may not be severed from the rest of the provisions in section 503A, and held that section 503A is invalid in its entirety. The court's mandate issued on May 7, 2001. As a result, section 503A is invalid in the States and territories that comprise the Ninth Circuit (California, Oregon, Washington, Arizona, Montana, Idaho, Nevada, Alaska, Hawaii, Guam, and the Northern Mariana Islands).

The Solicitor General's Office in the Department of Justice is responsible for determining whether petitions for *certiorari* should be filed in cases involving constitutional challenges to Federal statutes. The matter is under consideration, and the deadline for filing a petition for *certiorari* in this case is July 26, 2001. Because the question of Supreme Court review remains pending, FDA has not yet determined how the Ninth Circuit's decision will affect FDA's enforcement of section 503A in the States and territories outside the Ninth Circuit.

Question 6. FDAMA allowed for data from one adequate and well-controlled clinical investigation to serve as substantial evidence of a drug's effectiveness. Are you aware of any instance in which only one clinical trial was used to prove effectiveness?

Response. FDAMA allowed for data from one adequate and well-controlled clinical investigation and confirmatory evidence to serve as substantial evidence of a drug's effectiveness. CDER and CBER have approved several products based on this provision.

For example, CDER has approved:

- Lamictal (lamotrigine) was approved on August 24, 1998, for the treatment of Lennox-Gastaut Syndrome based on a single adequate and well-controlled trial and confirmatory evidence.
- Femara (letrozole) was approved on January 10, 2001, as a first line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer on the basis of a single, adequate and well-controlled trial and confirmatory evidence.

In order to meet the requirements of FDAMA, FDA issued a Guidance for Industry entitled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." This guidance demonstrates FDA's willingness to work with sponsors to help them plan drug development programs that are sufficient to establish effectiveness without being excessive in scope.

CBER has approved:

- TNKase (Tenecteplase, licensed June 2, 2000) for reduction of mortality associated with acute myocardial infarction.
- Synagis (Palivizumab, licensed June 19, 1998) a monoclonal antibody indicated for preventing serious lower respiratory tract infections caused by respiratory syncytial virus (RSV) in premature infants and those with lung disease.

Question 7. It seems that the drug manufacturing changes provisions of FDAMA have been used extensively by both drug and biologics manufacturers. Is it your belief that this will reduce the cost of producing drugs without compromising safety and effectiveness?

Response. Yes, we believe that the manufacturing changes provision has allowed the industry to produce products more efficiently thereby reducing costs, without compromising the safety of the products.

Question 8. Has there been much dissemination of off-label information pertaining to drugs and devices, or has litigation discouraged this?

Response. We do not have a systematic method to track the trends in the dissemination of off-label information and, therefore, do not know if dissemination of this information has been discouraged.

Question 9. Recently the FDA finally came out with its "least burdensome" Draft Guidance which should lead to more predictability in medical device reviews because FDA must demand no more than the "least burdensome" scientific proof for effectiveness. Why did it take the FDA three and one-half years to develop this Draft Guidance when it was such an integral part of FDAMA?

Response. The recent draft guidance that FDA issued is the latest of a number of documents the Agency has shared with the public to describe its approach to implementing the principles and concepts of the least burdensome provisions. Earlier documents were revised and modified in response to industry concerns and this latest draft guidance is partly the result of Agency participation in an industry-working group. Although this draft guidance was issued recently, CDRH has been working to put least burdensome processes and procedures into place every since FDAMA was passed. See response to number 10 below.

Question 10. What steps will FDA take to ensure that device reviewers are consistently implementing the least burdensome concept when conducting device reviews?

Response. The Agency has worked diligently with industry and staff toward the goal of obtaining the right information to support submissions—no more, no less. Activities have included a CDRH-wide working group on least burdensome issues, development of a web page containing up-to-date information, http:\\www.fda.gov/cdrh/modact/leastburdensome.html, a CDRH-wide (the first) web cast was held to engage staff and training has been held for all device review staff and advisory panel members.

Furthermore, CDRH internal tracking documents and correspondence have been changed and continued to be updated to embrace this concept, a working level appeals process has been established and a questionnaire for customer feedback has been developed. Finally, as you stated, the draft guidance entitled, "The Least Burdensome Provisions of FDA Modernization Act of 1997: Concept and Principles" has been posted on the web.

Question 11. Since passage of FDAMA, how many medical devices have been assigned expedited review? What steps do you take internally to ensure that these de-

vices designated for priority review receive the resources necessary for a timely review?

Response. The Agency continues to maintain a high level of premarket performance with all of its application types. Of the applications reviewed, many involved medical breakthrough devices that will provide significant improvements in-patient care. Since passage of FDAMA, CDRH has assigned 26 applications for expedited review. FDA always places special emphasis on getting these novel products through the process as soon as possible without compromising patient safety.

Question 12. Has the FDA taken advantage of its authority under FDAMA to contract out to appropriate experts parts of submission for review of devices? If the FDA has not contracted out part of device reviews, why not?

Response. When funding levels and circumstances permit, FDA has used its authority to contract with outside technical expertise when such expertise was needed. For example, in FY 2000, FDA hired 70 Special Government Employees to participate on the medical devices advisory committees. FDA has also contracted with the Oak Ridge Institute for Science and Education fellowship program to recruit experts to participate in reviews. The Agency will continue to contract with other experts when the need arises.

Question 13. The FDA just recently expanded the third-party review provisions of FDAMA to every class 11 device allowed under the law. Why was this decision only recently made? Is it true that since FDA made this change the number of companies seeking third-party review has increased?

Response. FDA met all its statutory requirements in implementing the third party provisions of FDAMA. This included publishing standards for third party review, reviewing applications for third party review, accrediting third party reviewers, and publishing guidance about devices that were eligible. FDA determined that the initial list of devices should be those that met the statutory criteria and had guidance or consensus standards that could support review. This was to develop experience with the program to ensure that there was consistency among third party reviewers and timely review by FDA following the third party recommendation. FDA has been working with industry trade groups to encourage wider use of this provision. Since implementation, devices eligible for third party review has grown to 674 eligible devices. Preliminary numbers for 2001 indicate that the number of third party reviews will increase to about 90.

Question 14. Could you explain in greater detail how the Sentinel System for medical device user facility reporting worked, and whether this pilot pro gram proved effective?

Response. The pilot for the sentinel system was called DeviceNet. After recruitment of a purposeful sample of user facilities in the Washington D.C. metropolitan area, North Carolina and Boston, eighteen hospitals and six nursing homes agreed to participate in the pilot. Facilities were trained in the requirements of the Safe Medical Devices Act (SMDA) and in participation in the project. Barriers to reporting (identified in earlier focus groups) were eliminated or reduced as much as possible. For example, all reports went to a third party (contractor); the participants were given regular feedback in the form of a newsletter, direct contact with FDA as desired, and other FDA communications; participants were allowed to report via phone and given assistance in completing the form and the coding. Participants were asked to report as required under SMDA (mandatory reports) but also to report incidents that had the potential for harm (near miss).

During the year long pilot, CDRE received approximately 300 reports, but only from the hospitals. This averaged about 16 reports per hospital. (Currently, FDA receives, on average, less than one report per hospital per year.) About half of the reports were "voluntary"—not required under SMDA—and a third of those "voluntary" reports were considered "urgent" as rated by FDA nurse analysts. This suggested that eliminating or reducing barriers to reporting could increase reports and that voluntary reports are important for FDA in carrying out our public health mission.

These results and additional detail and discussion can be found in the Agency's report submitted to Congress in August of 1999, "Designing a Medical Device Surveillance Network." (This report is on FDA's website at http://www.fda.gov/cdrh/postsurn/medsun.html). CDRH has also done some pilot work to further investigate how to overcome the apparent resistance of nursing homes to reporting to FDA.

In addition, the Medical Device Surveillance Network (MeDSuN) is being designed to benefit from what we learned in the DeviceNet. We hope to begin data collection on this project in 2002.

Question 15. Is it FDA's opinion that greater collaboration between FDA and industry has in any way compromised patient safety? Do you feel that the collaboration embodied within FDAMA has led to better decision-making within FDA?

Response. Greater collaboration between FDA and the industry has been very helpful. It ensures that the industry research is scientifically sound, relevant to the regulatory issues that must be addressed, and is consistent with human subject projection requirements. It provides FDA with a better understanding of the scientific base used in regulatory decisions. Such collaboration has enhanced consumer protection and safety; not compromised it.

Increased collaboration has resulted in clinical studies that are more likely to yield readily interpretable data, thereby limiting the number of individuals needed for study. Such collaboration helps assure adequate attention to safety issues; for example, because the numbers of meetings with manufacturers has increased, the quality of submissions has improved.

Good decision making relies on the best available information and on a clear understanding of the issues. To the extent that FDAMA has improved communication between industry and the Agency, it has facilitated Agency decisions.

Collaboration also has enhanced patient safety and led to better management of risk while still providing benefits to consumers. The Agency has collaborated with industry on a case-by-case basis to develop systems to manage risk for drugs that have higher risk potential but clearly offer benefits to patient groups that have no alternative therapies available.

One example would be Propulsid (cisapride) that was approved in 1993 for the treatment of nocturnal heartburn due to gastroesophageal reflux disease (GERD). The sponsor worked with the Agency to implement labeling changes and develop educational programs to help assure the safe and appropriate use of Propulsid after receiving reports of serious adverse events associated with the use of the drug. After seeing no decrease in adverse events after these changes had been implemented, in April 2000 the sponsor announced that the product would no longer be available through pharmacies after August 2000. This provided physicians and patients time to explore other treatment options to control the patient's disease. The sponsor and the Agency collaborated on structuring a program whereby patients who failed other treatment options and who met the criteria would be eligible to receive the product through an investigational limited access program.

Question 16. Are you aware of any petitions for health claims filed after passage of FDAMA which were published in the "Federal Register" but not finalized within 18 months of FDA's receiving the petition?

Response. To date, all health claim petitions filed after passage of FDAMA for which a proposal was published in the *Federal Register* have been finalized within 18 months of FDA's receipt of the petition. Two such petitions are currently pending. Both were submitted to FDA in February 2000. Because of their similarity of subject matter and proximity of submission, they are being handled in a single rulemaking action. FDA published an interim final rule for both of these petitions, rather than a proposal. Hence, manufacturers are currently able to use the claim even though rulemaking has not been completed.

Question 17. In early 1999 the FDA issued and advanced notice of proposed rulemaking to revise regulations regarding the labeling of foods treated with ionizing radiation. When will the FDA undertake and complete the rulemaking on labeling of irradiated foods?

Response. FDA received over 5500 comments on the labeling Advance Notice of Proposed Rulemaking (ANPR) and is currently in the process of evaluating the comments. The Agency intends to conduct focus groups and gather information from other contemporary surveys and studies. The purpose is to help the Agency better understand how the current label is perceived by consumers and what messages would be perceived as properly informative but not as a "warning," with the goal of developing alternative labeling that can reasonably be proposed. If these efforts are successful, FDA's goal is to develop a proposed rule on food irradiation labeling.

Question 18. Do you believe the "radura" symbol which is used on irradiated foods gives rise to consumer anxiety,

Response. Based on our preliminary review of comments received to the ANPR, the "radura" symbol in the absence of accompanying irradiation information had no specific meaning to commenters. The Agency intends to further explore consumers understanding of the "radura" symbol in its focus group research (noted above).

Question 19. What action has the FDA taken to assess and evaluate the impact on human health from dairy products produced by cattle injected with recombinant bovine growth hormone? Please provide a detailed explanation of your analyses and conclusions about the safety to humans from such dairy products.

Response. In 1993, following an extensive review of the data to support the safety and effectiveness, FDA approved the first animal drug containing recombinant bovine growth hormone (rhGH)—Posilac. A copy of a report FDA's Center for Veteri-

nary Medicine (CVM) published about that approval can be found on the FDA website at http:\\www.fda.gov/cvm/index/bst/RBRPTFNL.htm.

Since that approval, the Agency has no new data to indicate any negative impact on human health from using rhGH in dairy cattle. In fact, last year, FDA responded to a citizen petition filed, requesting that Posilac be removed from the market "based on new evidence" that the produce poses "serious health consequences for human consumers." In our denial of the petition, the Agency affirmed there was no evidence that the use of Posilac posed human health concerns. A copy of the Agency's response can be found on FDA's website at http:\\www.cvm/gov/efoi/citpet.pdf.

In very brief summary, the petitioner charged that:

1) a published study demonstrated that IGF-1 (a normal component of both human and bovine milk) was absorbed from milk and posed a risk of cancer;
2) the sponsor of Posilac altered the manufacturing process for the product after approval, thus invalidating the safety and effectiveness data in the application; and,
3) FDA had failed to review a food safety study or a portion thereof, which demonstrated that rbGH was unsafe.

In response, the Agency reviewed the study submitted by the petitioner and concluded that his interpretation of the study was inconsistent with other published and unpublished data, as well as the findings of the Joint Expert Committee on Food Additives of the World Health Organization which had found rbGH to be safe in two separate reports in 1992 and 1998.

The Agency rereviewed portions of the manufacturing component of the rbGH application and collected records from the sponsor related to investigational batches of Posilac. The rereview confirmed that the manufacturing change did not invalidate the safety and effectiveness data because it resulted in inconsequential changes to the formulated rbGH product. That is, the product that FDA approved was the same as the product on which the safety and effectiveness studies were conducted. The purportedly unreviewed portion of the food safety study had, in fact, been previously reviewed by the Agency and had been determined not to demonstrate any lack of safety of rbGH and the Agency reaffirmed that finding in the response to the petition. In addition, FDA responded to a second citizen's petition related to rbGH that can be found at http:\\www.fda.gov/ohrms/dockets/dailys/00/jun00/062700/pnd 0001.pdf.

Question from Ms. Eshoo:

Question 20. Despite extensive scientific evidence demonstrating serious risks associated with reprocessing of single-use medical devices - including several studies conducted by the Agency itself - FDA has failed to meaningfully enforce key patient safety provisions of the FD&C Act. It took substantial congressional and public pressure to force FDA to finally publish enforcement guidance on regulation of this potentially dangerous practice. Yet, I remain concerned that this guidance, while a step in the right direction, continues to permit the use of many unsafe reprocessed devices on American patients. Now that FDA has made its intention clear to conduct pre-market reviews of reprocessed medical devices, has the Agency received any submissions from reprocessors or hospitals?

Response. On February 15, 2001, CDRH received five premarket approval applications (all from third party reprocessors) for cardiac ablation catheters. CDRH is currently reviewing and intends to apply the same standards to these submissions as it does to all others. To date, we have not received submissions from any hospitals.

Question from Mr. Strickland:

Question 21. This question relates to the inability of clinicians to gain FDA approval for the use of thrombolytic therapy for peripheral vascular indications. These agents (Urokinase, rt-Pa and Reteplase) were each indicated for coronary artery problems (although Urokinase has been unavailable and will not be released until 2002). However, clinicians have been forced to use thrombolytic agents "off-label" for peripheral artery problems. The clinical trials 'required by the Center for Biologics have relied upon statistical assumptions that obligate the study of thousands of patients. Although such trials are possible for coronary artery problems, the smaller market and greater complexity of the procedures in the peripheral vessels renders such trials impossible to execute. Moreover, thrombolytic therapy is considered to be a "standard of care" for many patients with peripheral arterial occlusions. In this regard, it is difficult to enter such patients into the randomized trials required by CBER.

FDA has allowed devices a PMA pathway for device trials that are not randomized and based on comparisons to what constitutes little more than "historical con-

trols." For example, the approval process for the Ancure and AneuRx endovascular grafts. CBER has not been so conciliatory for thrombolytic drugs.

Given that other decisions of the Agency have allowed approval based on less rigorous statistics, is it possible to allow the trial with relaxed criteria to serve as a foundation for approval of agents already in use for other indications?

Response. While it is true that different trial designs, sample sizes, and statistical analyses may be used to satisfy the legal standard for approval of a drug, in all cases the data must meet the standard of substantial evidence from adequate and well-controlled trials that the drug is safe and effective. It undoubtedly is easier to meet the legal standard for approval for some products and indications than for others. Where meeting the approval standard is particularly difficult, careful exploration of proposed approaches to meet the standard is warranted, however, the standard remains and the approach used must be scientifically valid.

Differences in approaches to studying different products frequently arise due to differences in the indication or the products. Thus, a design or analysis that is suitable for one product and indication may not be suitable for another. For example, historical control designs may be useful where the historical control patients are well characterized and well matched to the study patients, concomitant therapy has not changed over time, the historical outcomes are highly consistent and predictable, and the drug effect is large. However, historical control designs may not be useful when these criteria are not met.

The experience with devices, cited in the question, involved very different settings. One of two specifically mentioned devices is the "Ancure" device, marketed by Guidant. This Class II device is a balloon catheter for use in illiac arteries. It is marketed under a 510(k)-notification mechanism, as being "substantially equivalent" to a marketed predicate device, a standard very different from that for new drug approval. The other specifically noted device is "AneuRx," marketing by Medtronic is a Class III device. The medical indication, infrarenal aortic aneurysms, is quite different from the indication being sought by thrombolytics, peripheral arterial obstruction (PAO).

FDA is quite interested in having the use of thrombolytics for PAO appropriately assessed and, if appropriate, labeled so that physicians and patients can know they are using a safe and effective regimen. CBER has worked actively for many years with several manufacturers of thrombolytic agents developing clinical research programs for this indication. CBER has been open to a variety of approaches to demonstrate clinical efficacy in this setting. These approaches include randomized, placebo-controlled studies, randomized dose-ranging studies; studies which seek to demonstrate a clinical benefit of the most major importance (death and/or amputation) and studies which seek to demonstrate benefits of a somewhat less compelling nature. While CBER has had discussions with manufacturers to consider the use of historical controls in this setting, no manufacturer has come forth with adequate evidence to date to establish that a trial with a historical control comparison would provide valid evidence of efficacy in this setting.

Clinical trials to date have largely had no concurrent controls and drawing clear conclusions is difficult or impossible. While there is a general impression in the medical community that thrombolytics are likely to be useful in this setting, the data on any specific dose-regimen with any specific agent are rather limited. The published literature makes clear those elements of safety, and likely efficacy, may be very dependent upon dose and regimen.

Questions from Mr. Waxman:

Question 22. During FDA rulemaking on pediatric studies and during hearings and deliberations on this rulemaking, a number of drugs were noted by witnesses, committee members, and the FDA as important drugs needing pediatric study. How many of the on-patent drugs have received a written request for pediatric studies? IF not all have received such a request, please explain why not.

Response. Enclosed is a copy of the "10 drugs most widely prescribed in pediatric age groups in 1994 for which the label carried no directions for use" (Pediatric Exclusivity Report to Congress, Appendix B, Table 7, page 37).

Table 7

10 Drugs most widely prescribed in pediatric age groups in 1994 for which the label carried no directions for use

Drug	Treatment Use	Number of uses	Study proposal submitted by sponsor	Exclusivity or patent life
Albuterol Inhalation solution.	asthma	1,626,000 times to pediatric patients under 12	No[1]	No
Phenergan	allergic reactions	663,000 times to pediatric patients under 2	No	No
Ampicillin Injection	infection	639,000 times to pediatric patients under 12	No	No
Auralgan otic solution.	ear pain	600,000 times to pediatric patients under 16	No	No
Lotrisone cream	topical infections	325,000 times to pediatric patients under 12	Yes	Yes
Prozac	depression and obsessive compulsive disorder.	349,000 times to pediatric patients under 16	Yes	Yes
Intal	asthma	solution prescribed 109,000 times to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5.	Yes	Yes
Zoloft	depression	248,000 times to pediatric patients under 16	Yes	Yes
Ritalin	attention deficit disorder and narcolepsy.	226,000 times to pediatric patients under 6	No	No
Alupent	asthma	84,000 times to pediatric patients under 6	No	No

[1] Currently labeled for patients >2.

Of the top ten drugs, six products had no existing exclusivity or patent protection and four products (Prozac [fluoxetine], Intal [cromolyn sodium], Lotrisone [betamethasone/clotrimazole] and Zoloft [sertraline]), had existing exclusivity or patent protection. The Agency has issued Written Requests (Aa) for these latter four products.

Question 23. Of the most complete list of "approved drugs for which additional pediatric information may produce health benefits in the pediatric population", how many of the on-patent drugs have received a written request for pediatric studies? If not all have received such a request, please explain why not.

Response. The most current list of "approved drugs for which additional pediatric information may produce health benefits in the pediatric population" updated in May 2001, identifies 426 drugs on the priority section of the list. Of these, 103 have existing patent protection or exclusivity and have received a written request. Of the remaining products on the list, many have existing patent protection or exclusivity. To use our resources in an effective manner, we generally issue a written request after a sponsor submits a proposed pediatric study request. In some cases, we have issued written requests to an entire class of drugs after a template for a request was developed, for example, anti-hypertension drugs, drugs for depression/OCD, HIV drugs.

Question 24. Please provide a list of all approved drugs to which FDA has issued a written request for pediatric studies. Please note the manufacturer of the product and the date on which the request was issued. Please note whether the manufacturer has agreed or disagreed to the written request and the date on which the manufacturer responded. If the manufacturer has not responded please note that as well.

Response. As of May 2001, 157 approved active moieties have received a written request. We are providing at Tab B a list that identifies the active moieties, the manufacturers, and the dates on which the written request was issued. Manufacturers are not required to alert FDA as to whether or not they plan on pursuing the studies. However, based on our informal discussions with the manufacturers, we estimate that approximately 80 percent plan on conducting the studies.

This list contains confidential information not releasable to the public, and we ask that the Committee not make public or publish as part of this hearing record, the enclosed information.

Question 25. What is FDA's estimate of the mean, median, and mode of the cost of the pediatric trials requested in a written request for a company?

Response. As of May 2001, 191 WRs have been issued. In these WRs, 421 studies have been requested. The types of studies and number of each requested are as follows: efficacy/safety—138; PK/safety—125; PK/PD—36; safety—83; and other—39. While we are unable to provide you with a mean, median, and mode for the cost of the studies, we can estimate that the cost ranges from $500,000 to $4,000,000 per study. Efficacy studies would be at the top of the range while the cost of a PK

study would be at the lower end of the range. In addition, some sponsors have to create the necessary infrastructure to do these studies, and this adds to the sponsor's costs.

Question 26. What is the FDA's estimate of the mean, median, and mode of the number of trial participants requested in the studies requested in a written request for a company?

Response. Again, while we are unable to provide you with a mean, median, and mode of the number of trial participants, we can tell you the following. As of May 2001, the Agency has requested 421 studies. Of these 421 studies, 233 specified the number of patients to be studied. The projected total number of patients for these 233 studies is >23, 536 patients. The remaining 188 studies requested a sufficient number to meet the study's objective, e.g., sufficient number to characterize the pharmacokinetics, powered to demonstrate a specified difference. We have not projected the total number of patients for these other studies.

Question 27. How much additional funding and how many additional personnel would it require for FDA to process SNDA's for pediatric use at the same pace as NDAs? How much additional funding and how many additional personnel would it require for FDA to process all SNDA's at the same pace as NDA's? How much additional funding and how many additional personnel would it require for FDA to process all ANDA's at the same pace as NDA's?

Response. All pediatric clinical supplements are currently reviewed at the same pace as NDAs (12 months for a standard review or six months for a priority review). Any additional resources would allow us to more efficiently review the applications we currently receive, including pediatric supplements, abbreviated NDAs, and all other supplemental applications.

Question 28. Inasmuch as the approval of ANDA's can greatly reduce the cost of prescription drugs to the Nation in general and to government programs in particular, why has the Administration not requested sufficient funding and personnel to process all ANDA's at the pace of NDA's?

Response. The generic drug program was granted a $1.2 million increase in FY 2001. In addition,we continue to refine the review process to increase efficiency. The number of new staff hired in the last fiscal year are now fully trained and are demonstrating high levels of productivity. There are, however, certain factors outside of our control that would prevent complete adherence to the 180-day time frame. These factors include the need to adhere to the review queue review structure, timeliness of inspections of the manufacturing plants, and legal issues such as lawsuits and Citizen Petitions. All chemistry reviewer vacancies are currently filled. We continue to examine every aspect of the review process to try to identify problem areas to be addressed. We also plan to revise the current system for amendment designation (major versus minor) to improve total review times. Other changes are also being explored. While we did not request a specific increase for generics in FY 2002, this office will benefit from the requested increase for pay raises of approximately $2,000,000.

Question from Mr. Whitfield:

Question 29. Would FDA be amenable to employing a mandatory premarket GRAS notification procedure, modeled on the voluntary GRAS notification procedure already being implemented, as a means of expanding the permitted use of a food substance affirmed as GRAS with specific limitations under 21 CFR sec. 184.1(b)(2)? What would be the most expeditious way of effectively implementing such a new procedure?

Response. The rulemakings that established § 184.1(b)(2) itself, as well as the specific regulations promulgated in accord with § 184.1(b)(2), were put in place through notice-and-comment rulemaking. FDA must follow its own regulations, and must evaluate the safety of a new substance currently subject to § 184.1(b)(2) using notice-and-comment rulemaking.

Generally recognized as safe (GRAS) ingredients, unlike food additives, are not subject to statutory premarket approval requirements. When the Agency affirmed as GRAS the current uses of ingredients under § § 184.1(b)(2), it determined that other uses outside the scope of the approval would be food additive uses. Thus, FDA would need to consider whether the new uses of substances currently subject to § 184.1(b)(2) are GRAS and, if so, consider whether it would be appropriate to amend § 184.1(b)(2) and/or the current approvals under § 184.1(b)(2). The Agency would be open to discuss with any interested party the best way to approach a given review.

Thank you again for making this a part of the public record. If you have further questions, please let us know.

MELINDA K. PLAISIER
Associate Commissioner for Legislation

Enclosures

cc: The Honorable Sherrod Brown
Ranking Minority Member
Subcommittee on Health
Committee on Energy and Commerce

NATIONAL ORGANIZATION FOR RARE DISORDERS, INC.
June 11, 2001

The Honorable MICHAEL BILIRAKIS, *Chairman*
House Energy and Commerce Subcommittee on Health
United States House of Representatives
2369 RHOB
Washington, D.C. 20515

Attn: Brent Del Monte

DEAR MR. CHAIRMAN: Thank you for the opportunity to respond to questions arising from my testimony before the House Committee on Energy and Commerce Health Subcommittee on May 3, 2001 regarding the reauthorization of the Food and Drug Administration Modernization Act (FDAMA), as well as the pediatric exclusivity provision, which in January 2002.

Question 1: In your written testimony you lament the fact that more new drugs are being introduced in the United States before they're introduced in the rest of the world. Is it your belief that individuals with rare disorders would benefit from having drugs to treat their conditions introduced elsewhere before they're introduced in the United States?

Response: In my May 3rd testimony to the Subcommittee, I pointed out that in 1988 only four percent of new drugs were first approved in the United States, but by 1998, that figure had risen to 66%. I did not "lament" that fact, but simply pointed out that there are fundamental risks associated with being "first out of the gate." In her defense of the many drug withdrawals ordered by the FDA, Dr. Janet Woodcock, FDA's Director of CDER, has blamed those withdrawals on the fact that we are now the first country to market most new drugs and therefore adverse events tend to appear here before in the rest of the world. Inherent in this fact, however, is my argument that none of the withdrawn drugs were life saving drugs, and they probably should not have been rushed to the American without additional FDA review.

Regarding whether individuals with rare disorders would rather see "orphan drugs" marketed in other countries before the United States, obviously the answer is no. However, it is important to note that most orphan drugs are lifesaving medicines for largely untreatable diseases that have been afforded priority review from the FDA, and they have been approved first in the United States (since the *Orphan Drug Act* was enacted in 1983).

NORD has always advocated for speedy review of lifesaving drugs, both orphan and non-orphans. My testimony does, however, lament the fact DUFA has expedited review of many nonessential drugs that are *not* important medicines for serious and life threatening diseases. We feel strongly that the FDA should take more time to review non-essential drugs because they may represent risks to relatively healthy people, or to those who have other satisfactory treatment alternatives.

Question 2: In your testimony, you criticize the fact that the FDA negotiates drug labels with manufacturers, and you say the FDA should be given authority to order immediate labeling changes. But isn't it true that the FDA already has this authority? The FDA already has the ability to keep off the market new drugs if the FDA doesn't approve the label, and they have the ability to seize any drugs which are misbranded, don't they?

Response: Before responding to this question, I would like to reiterate NORD's strong support for the testing of drugs used in the pediatric population. NORD will work with members of the Subcommittee to ensure reauthorization of the pediatric exclusivity provision, but we do have some concerns regarding specific problems that have arisen since 1997.

In response to Question 2, of course the FDA has authority to keep drugs off the market if they do not agree with the manufacturer's labeling. The agency also has

the authority to seize misbranded drugs when warranted. But the fact remains that of all the pediatric studies submitted, only about 14 actually have been relabeled.

To solve this problem we suggest that the FDA be given authority to require manufacturers to relabel their drugs for pediatric use within a very specific timeframe even if the company does not agree with the language that the agency believes is scientifically justified. Alternatively, the FDA could be given authority to withhold exclusivity if a manufacturer refuses to add pediatric information to the drug's label. We feel it is critically important for pediatricians to have access to pediatric prescribing information, and *exclusivity should be directly tied to the labeling requirement.*

Question 3. The Elizabeth Glaser Pediatric AIDS Foundation, in a letter signed by Dr. David Kessler, says the pediatric exclusivity provision should be reauthorized because a one-half of one percent increase pharmaceutical costs "is a legitimate price to pay to ensure our children's well being." Do you disagree that a one-half of one percent increase in pharmaceutical costs is a legitimate price to pay for our children's well being?

Response. The legitimacy of a one-half of one percent price increase depends on the person who is paying. To an insured person, the price may not be significant, but to an uninsured person or an elderly Medicare recipient who pays cash for prescriptions, any increase would be catastrophic. If Medicare paid for prescription drugs, this probably would not be an issue, except for insurance companies who blame their annual price increases on the escalating costs of prescription drugs.

The real issue is that some drug companies receiving pediatric exclusivity are reaping rewards far greater than their investment in pediatric clinical trials. The financial rewards can sometimes be so great that they focus on their research on only the most lucrative drugs, rather than the drugs children need most. Nevertheless, my testimony clearly supports reauthorization of the pediatric exclusivity law with some modifications.

I hope these answers to your questions are satisfactory. I will be pleased to answer any further questions you may have.

Sincerely,

ABBEY S. MEYERS

cc: Diane Dorman
Sherrod Brown, Ranking Member
John Ford, Minority Counsel