

THE NEED FOR FDA REGULATORY REFORM TO PROTECT THE HEALTH AND SAFETY OF AMERI- CANS

HEARING

BEFORE THE

SUBCOMMITTEE ON NATIONAL ECONOMIC GROWTH,
NATURAL RESOURCES, AND REGULATORY AFFAIRS
OF THE

COMMITTEE ON GOVERNMENT
REFORM AND OVERSIGHT
HOUSE OF REPRESENTATIVES

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FRIDAY, JUNE 9, 1995

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON NATIONAL ECONOMIC GROWTH,
NATURAL RESOURCES, AND REGULATORY AFFAIRS,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Norristown, PA.

The subcommittee met, pursuant to notice, at 10:07 a.m. in Courtroom B, third floor, Montgomery County Courthouse, Main and Swede Streets, Norristown, PA, Hon. David M. McIntosh (chairman of the subcommittee), presiding.

Present: Representatives McIntosh, Fox, Tate, and Peterson.

Ex Officio Present: Representative Clinger.

Also present: Representative Walker.

Staff present: Mildred Webber, staff director; Jon Praed, chief counsel; Karen Barnes, professional staff member; David White, clerk; Judy Blanchard, deputy staff director for the Committee on Government Reform and Oversight; and Bruce Gwinn, minority senior policy analyst.

Mr. MCINTOSH. The Subcommittee on National Economic Growth, Natural Resources, and Regulatory Affairs is convened to order.

It is a pleasure to be here today in this part of Pennsylvania. I appreciate my vice chairman, Mr. Fox, making all the arrangements for us. He has done a tremendous job.

Let me say to you here who are lucky enough to have him in Congress, he has been working very hard on our subcommittee and doing an excellent job of representing the interests and the needs of the people here in Pennsylvania.

I am also very pleased that with us today is the chairman of the full committee, Mr. Clinger, who has been guiding us on the subcommittee. He was kind enough to allow a freshman to chair one of his subcommittees and has been very helpful to me in setting up our committee and making sure that it works well and runs efficiently.

Also with us is Mr. Peterson, the ranking minority member, who is here from Minnesota. I also appreciate it, Collin, when you are able to join us. It shows that this is a bipartisan effort to look at regulatory problems and try to find solutions that will make it better for all Americans.

We have Randy Tate, who is a member of the committee from Washington State, and Mr. Bob Walker is going to be joining us later. He is chairman of the Science Committee, and I would ask unanimous consent that he be allowed to participate as an ad hoc member of this committee.

Seeing no objection, it will be so ruled.

Today the subject of our hearing is Food and Drug Administration regulations, particularly in the approval of new drugs and pharmaceuticals. The Food and Drug Administration plays a critical role in the health and safety of the American people and one that I believe all of us want to see continue and improve.

The FDA regulates more than \$1 trillion worth of products every year. That is about 25 cents on every dollar that is spent in America each year. The FDA regulates everything from the food we eat to the drugs we take to the cosmetics that we wear. Because of this critical role that FDA plays, it is appropriate that this new Congress takes a hard look at the agency to insure that the American people are receiving the best medical care with access to the latest breakthrough lifesaving drugs and devices.

As chairman of the House Regulatory Affairs Subcommittee, I have taken a look at that agency. I have reviewed very thoroughly the drug approval process, and I can report to you today that it is my opinion that the FDA is an agency that in many ways is out of control. Its disregard for the health of Americans suffering from treatable illnesses is in some ways shocking.

Today, thousands of Americans are needlessly suffering and dying because the agency has prevented them from receiving the latest, most effective medicines that are safe and effective for use. Because of the needless red tape and bureaucratic snafus and in some cases even intimidation, too many Americans are suffering needlessly, and the evidence of this is overwhelming.

New drugs require on average 12 years for approval in the United States, 100,000 pages of paperwork, nearly \$400 million in order to receive approval from FDA. Doctors are effectively prohibited by FDA from talking about the drug and the device manufacturers and using it for certain needs that may not have received approval by the agency even if they feel it is the best treatment for their patients.

American companies are moving overseas to countries like Ireland and the Netherlands to escape the heavy hand of FDA regulations. Trial lawyers have pressured the agency to delay new drugs and device approvals so they can profit from lawsuits, and special interest groups enjoy special access to the agency's inner circle that the rest of us simply do not have.

In my home district, a doctor mentioned to me that he is aware of a new insulin drug that has not been approved here in the United States which would greatly improve the treatment of diabetics, but it has been approved in Russia. He found it ironic that as we win the cold war, we cannot win the effort to get good, effective drugs for our patients here in this country.

The FDA has said that it performs its job relatively efficiently and cheaply, only \$3 per person per year, but I think today we will hear from many witnesses who are patients and doctors working with the drugs that they have approved, and we are indeed paying

a much higher price. In fact, too many Americans are paying a higher price of sacrificing the access to the best possible medical treatment that they may get.

I look forward to hearing the testimony today. Our panels will be first citizen witnesses and then a representative of the agency. We will get a chance to inquire into many of these regulatory problems.

Before beginning the hearing, let me turn to Mr. Clinger for any opening statement that he may have.

Mr. CLINGER. Thank you very much, Chairman McIntosh. At the outset, I would like to wish you a belated happy birthday. I understand you had a birthday yesterday.

Mr. MCINTOSH. Thank you.

Mr. CLINGER. I also commend you for coming to Pennsylvania and specifically coming to Congressman Fox's district because this is certainly a district that has a great interest in the whole question of regulatory reform, particularly as it relates to FDA because there is a very substantial presence of companies that are involved in producing drugs and other things for the industry which obviously has to bear a lot of these problems.

Also, I want to commend Mr. Fox for bringing the committee to your district and for your great concern for the problems that you have identified with regard to the issues that we are going to be looking at here today.

I am really pleased to join with you and Congressman Peterson and Congressman Tate to examine a host of FDA regulatory reform issues, including drug and medical device approval.

In the past few weeks, I have had an opportunity to talk with a number of Washington representatives about FDA regulatory reform, but today, and I think this is why these field hearings are so important, we have an opportunity to hear directly from some of those that are most impacted, such as the patients, doctors and companies, by the fact that we have these inordinate delays. All of these constituencies are trying to provide care for those who need it in an expedient and effective fashion.

The FDA, by its own estimates regulates one quarter of the consumer products—one quarter of the consumer products—in the United States. With over 9,500 employees and a budget of \$975 million annually, there are indeed serious concerns about the agency's ability to get the job done.

Despite frequent reform recommendations, it seems that most of the changes over the past 20 years have resulted not in a decrease, but in an increase in the agency's regulatory responsibilities.

There seems to be considerable delay in the drug approval process, which we are going to hear about this morning. During the 1970's, the average time for approval was 5 to 7 years. Today it is averaging somewhere between 10 and 12 years. We are going in the wrong direction in terms of product approval.

The time and the cost of development discourages companies from producing new and innovative drugs that may be beneficial to patients. It becomes an extraordinarily expensive proposition to do the research and bring to market these products. Excessive regulation, inconsistencies in regulations, too high costs and a lack of

focus by the FDA are all apparently stifling innovation and technology.

In addition to regulatory concerns, we need to look at how we can harness the private sector in the approval process using outside resources of experts for review. I think that would be perhaps a direction we could go that would perhaps do the most to expedite the procedures. By using private sector resources, we may be able to expedite the review processes at less cost.

I believe it would also be useful to look at how other countries are conducting drug approvals—as Chairman McIntosh mentioned, some are obviously moving faster, and we could do as well—and whether we should continue to apply our standards to other countries.

Clearly a top to bottom review of FDA's missions, goals and regulatory processes is sorely needed and long overdue. The status quo is costing us jobs, dollars and, most importantly, lives.

Mr. Chairman, I look forward to hearing the testimony from our witnesses today as an important part of the re-examination process and in your ongoing efforts to bring some sanity to the whole regulatory processes in this country.

I commend you again for holding the hearing, and I also am delighted that you came to Pennsylvania.

Mr. MCINTOSH. Thank you very much, Chairman Clinger. I greatly appreciate you participating in this hearing with us today.

Let me turn now to Mr. Peterson for any opening statement.

Mr. PETERSON. Thank you, Mr. Chairman. I will be brief so we can get on with the witnesses.

I again want to commend you and Chairman Clinger for your leadership on these regulatory issues. I think we are making a little progress, but I think it will be quite a battle.

In the district that I represent, we do not get involved too often with the FDA, which I think is fortunate, given some of the slowness of the process. There has been some talk of them giving more power to the FDA over food inspection, which I shudder to think about, given how some of this works.

I do not know a whole lot about the FDA. From what I read about it, it is similar to what I do know something about, and that is the bureaucracy that we have in the House and in the Government on computers where you cannot get the leading technology because the bureaucracy is in the way. It seems like we had kind of a similar situation here with the FDA on some of these issues.

I have kind of taken this philosophy the longer I am in Congress. I have decided that I am not going to believe anything unless I see it firsthand.

I had an opportunity to go over to Israel. As part of that trip we got to go to some businesses. What I was really struck by in that tour was how many medical companies we have in Israel because they could not get approval for their products here in the United States. These were American companies, American scientists that have gone to Israel because they are completely frustrated by the situation that is going on here in the United States.

Clearly, this is something that we have to deal with. What is going on is unacceptable. As I understand it, the Department has

some reinvention plan which has some good points, but frankly I am a little skeptical. I am not sure that it goes far enough.

I am looking forward to working with you, Mr. Chairman, and Mr. Clinger and Mr. Fox, who is working on a bill that I would be happy to help him with and see if we can untangle some of this.

Thank you for inviting me to the hearing.

Mr. McINTOSH. Thank you very much, Mr. Peterson.

Mr. Fox, thanks for setting this all up. We are delighted to be here.

Mr. FOX. Thank you, Mr. Chairman. I appreciate the opportunity to speak about this issue and to have each of you be here today.

Frankly, as this committee is the one charged in this One Hundred and Fourth Congress with regulatory review, I cannot think of a more important area for us to work on than the review of the FDA with regard to the accessibility of life extending and lifesaving drugs here in the United States.

I extend a personal welcome to all who have joined us. I see that Congressman Walker has also joined us. I am very pleased that the chairman of the Science Committee is here. I welcome you to Montgomery County, the 13th Congressional District of Pennsylvania, which I am honored to represent.

Mr. Chairman, I am pleased that we have organized today's hearing on this issue of significance. As was aptly described in a recent article by Carl B. Felbaum, president of the Biotech Industry organization, lifesaving new drugs do take too long to reach the people who need them.

In my district alone, I have heard many a compelling story from constituents afflicted with cancer, Lou Gehrig's disease, epilepsy or AIDS who speak of the difficulties in accessing the medicines they need because the approval process in our country is so prolonged and in effect they have to turn to other countries where the products are available.

We are fortunate to have some of the individuals with us today. I look forward to hearing their experiences, hopefully to bring about the positive change they want and we want.

It is important to note that the Food and Drug Administration serves a valuable purpose in maintaining high safety and efficacy standards. However, it is also important to recognize that the FDA's actions directly effect the lives of patients and the ability of physicians to provide state-of-the-art care for their patients.

As Chairman McIntosh eloquently commented previously, the period beginning with the initial testing of a drug and continuing until final approval by the FDA can require 7 or 12 years before it reaches the shelves.

Furthermore, the FDA regulates businesses that produce 25 percent of America's gross national product, so the agency's actions also impact our country's well being. The pharmaceutical industry is an excellent example. The United States leads the world in discovery of new drugs, yet all too often these drugs are available overseas first.

The United States is far and away the leader in biotechnology, but many biotechnology firms are moving clinical trials overseas because of the red tape imposed on them by the FDA. These are

very troubling trends that do not bode well for the economic future of the United States or its health future.

In the 13th Congressional District of Pennsylvania alone, we have many pharmaceutical and biotech companies. Together they employ more than 11,000 people. We would not want to see any of these constituents lose their jobs because the FDA regulation is prompting companies to conduct much of their work overseas.

Americans want safe medicines. They want a strong FDA that will keep unsafe products off the market, but I believe—we believe—they want to see more emphasis on the value of giving patients quicker access to safe and effective new medicines.

Those with life threatening diseases want to take control of their own illness. We need to break down the barriers to experimental drugs, to approve new drugs as fast as possible, to have free flow of information about those drugs. We want to make sure we correct the regulatory spiral which has caused us to have restrictive procedures.

We need to revise the Food and Drug Administration's mission statement and eliminate unnecessary paperwork. We need to provide the FDA the incentives to increase the availability of new life extending and lifesaving drugs. We need to protect Americans without unduly restricting innovation. To some, the FDA has been Fostering Delay of Approvals. We need to change that to Facilitating Drug Access.

I say to you, Mr. Chairman, that I appreciate the opportunity to have these hearings hopefully to move ahead to a system that is going to improve access to our consumers, while still maintaining quality. I thank you for this opportunity.

Mr. McINTOSH. My pleasure. Thank you very much, Mr. Fox.

Chairman Walker has arrived. Thanks very much for coming over, Mr. Walker. I appreciate you joining us today. Earlier we passed a resolution making you an ad hoc member of this committee.

Mr. WALKER. I am delighted by that, Mr. Chairman. I am actually on a leave of absence from the committee as it is.

Mr. McINTOSH. Welcome back.

Mr. WALKER. I am glad to be back, and I am delighted to be with you here in Montgomery County today. We thank you for coming.

Mr. McINTOSH. Thank you.

Mr. Tate or Mr. Walker, do you have any opening statement?

Mr. WALKER. I have no opening statement. That was opening statement enough.

Mr. TATE. I would like to start by saying I would like to thank the chairman as well of this committee, Mr. McIntosh, and Mr. Clinger of the full committee and Mr. Fox with whom I have had the pleasure to work with as a fellow freshman. It has just really been an honor to work with him. He has been an aggressive, assertive, hard-working member of the committee, and he has done a phenomenal job.

I will keep my comments very brief because we are here to hear from the public and not the politicians, and that is what is so important about these public hearings. A number of the concerns have been brought up. We are going to hear from consumers, from industry, from the agency and some experts.

The thing that troubles me is many people are forced to go abroad, spend more money and may not even have the opportunity for the drugs at all because people are discouraged from investing their capital in the discovery of new drugs or medicines because of the fact that it takes so long.

Many times I think we need to look at changing some of our laws in regards to allowing drugs to be used for people that have life threatening diseases or a terminal condition. We need to look at exceptions or change in those particular laws.

The FDA has done a good job in some areas, but my local experience out in Kent, Washington, with Dr. Wright where the FDA had worked and come in before hours and knocked the doors down and came in and took things away such as vitamin B-12, which I cannot see as any risk to anyone. To me, that is outrageous. Those are the sorts of things that need to be investigated, and that is why we need to take a closer look. That is my personal experience. We need to change the process. We need more participation.

I look forward to hearing the individuals that are going to testify today. We truly can save more lives. I think we can save a lot of money, and we can make this a country where people can have access to the kind of medical treatment that they would prefer and think is appropriate for them in a cost effective and safe manner. I look forward to hearing from the public on this.

Mr. MCINTOSH. Thank you very much, Mr. Tate.

Let us turn now to our first panel of witnesses. Welcome. Let me say at the outset that we have several people who are here to testify today, and we also want to have a time period where we have an open microphone session to hear from additional witnesses. I will be fairly strict about asking people to keep their remarks to 5 minutes.

I am going to ask the timekeeper to use this clock right here to show a green light after about 3 minutes to give you time to start thinking about a summary of your statement and then the red light after 5 minutes.

Let me urge you to not use a prepared statement if you feel comfortable. It generally works better and you get your points across in fact more effectively is what I have found in listening to witnesses over the last few months. If you are at all comfortable with that, let me urge you to summarize the written statement.

The full statement will become part of the official record, and the written statement you have in addition to the 5 minutes will as well.

It is the policy of the full committee to swear in all of our witnesses, so if I could ask the first panel to please rise and raise your right hand.

[Witnesses sworn.]

Mr. MCINTOSH. Let the record show the witnesses have answered in the affirmative.

Thank you all for coming today. I know in many cases it was with some personal hardship. I look forward to hearing from you.

Our first scheduled witness was Beverly Zakarian, and she is not able to make it today. She is suffering from cancer and had a chemotherapy treatment yesterday and is not well enough to be with us. Her statement will be put into the record.

One of the things that the staff informed me that she was hoping we would be able to do is make more drugs available to help control the nausea that comes from chemotherapy so that that type of incident would not happen to her. Her statement will be here, and our best goes out to her. I hope she feels better as she struggles with that treatment.

[The prepared statement of Ms. Zakarian follows:]

CAN ACT 1

Mr. Fox, thank you for inviting me to offer my remarks to you and your distinguished colleagues this morning.

This is what's needed at the FDA: a can-opener-- to rip the lid off an agency that's been vacuum-packed for too long, impervious to public accountability or scrutiny, self-contained. It's time to open it to light and air-- and get rid of the rot inside.

I am here not to speak of my own experience ten years ago when I needed a cancer treatment drug that was not yet FDA-approved --although that's what first turned my attention to the FDA as the silent, but controlling, partner in the life of everyone with cancer-- but as the Executive Director of CAN ACT, a patient-advocacy organization whose mission has been identifying the FDA as a barrier to people who seek life-saving therapies to fight their disease.

I am not here to speak only of my own interest in having every possible new drug available to treat cancer, but to represent the interest of millions of people living with cancer in these proceedings.

Why should people who are fighting for their lives have to fight their government for the drugs they need to fight the disease?

Because the agency charged with the responsibility of protecting the safety of consumers has never understood that the stakes are different for people with life-threatening illness. It cannot comprehend that we do not want to be protected to death. It does not accept as a concept that a real risk of death from illness should give rise to different considerations, and greater flexibility, in drug approvals. It does not accept it because *politically* it never had to, but it was playing politics with my life, and the lives of other people with cancer.

I've been involved with the FDA just about as long as the present Commissioner, and a lot less profitably. I'm convinced that nothing but a can-opener will work. It will take brute force to reform the FDA, because neither reason, nor common sense,--not even humane considerations-- have made any difference in the past. There I have no reason to think they will in the future.

CAN ACT 2

And why not? Because too many true-believers are entrenched in the agency. It's not so simple a matter as rewriting regulations: there's a mindset against approval on the part of career employees and people who have been hand-selected to sit on Advisory Committees. Nothing but an entirely new structure, and new people, will make any difference.

So I would like to offer some directions for reform. Some of them are mutually exclusionary, but I present them as concepts for thought and discussion, not as carefully-wrought legislation.

First, that you separate the FDA from any functions in the area of drugs for life-threatening illness.

The FDA has amply demonstrated that its heart is buried deep in consumer protection. Some of what it has done is of benefit to consumers: Food labeling is more informative; fresh orange juice is either fresh or it's not. This is where the real interests of the Commissioner and his agency lie, and the need is there.

So be it. Change the FDA into the FA, and let us be protected zealously from contamination of our food supply by pesticides and herbicides; protected from rampant adulteration by food coloring and unnecessary cosmetic additives; from excessively hasty introductions into our food supply of genetically-engineered products that all carry with them the seed of penicillin-resistance, a time-bomb in the making for the health of the American people.

Then formulate a new, sensible, responsive agency for the D, on which so many lives depend.

Second, if that is not possible, separate the functions of the FDA so that it cannot both approve and regulate drugs.

When I was in the advertising industry in the seventies, it was mocked as "the league of frightened men." I would say that the advertising industry has nothing on the pharmaceutical industry. Why? Because there is so very much money at stake, and only one boss to answer to.

Let me tell you that drug companies were afraid to support *educational material* published by CAN ACT about clinical trials, about patient empowerment, about news of

newly-released anti-nausea drugs-- because they were afraid to be associated with me or my organization in the FDA's mind. Is that ludicrous? Yes, sadly, and all too believable. You and I both know the capacity of the FDA to punish a pharmaceutical company by sitting on their next drug application, by slow-tracking it. No matter that *people who are sick* might need the drug; this is how the FDA operates.

Third, force public accountability.

Advisory Committees are supposed to have a non-voting representative of the public, a consumer, participate in approval deliberations. That person should be sent to the FDA by the public, and must consult with her or his constituents, advising them of the issues and keeping people informed of the process.

Six years ago, I applied to become such a representative. What I learned was that public representation was a sham; the well-intended mechanism had been easily manipulated so the FDA could *appoint* "consumer representatives" that would parrot the party line, just as it appointed like-minded doctors to its panels. Two doctors and a lawyer have been "consumer representatives," each of them from the same Washington coterie. The two doctors had cancer, at least; the lawyer did not even that.

Thanks in part to my efforts, but mostly thanks to the much greater force of AIDS activism, *ad hoc* consumer representatives are now being seated, although I hear that this is a source of great anxiety and bitterness at the FDA. The current *ad hoc* cancer representative (appointed) is -- did you guess? -- a doctor!

Fourth, force the FDA to change its label designation structure.

This is a critically important issue that goes to the heart of the most important problem confronting people with cancer today: the issue of "off-label" use. Because the FDA approves -- "labels" -- drugs for use only in a very defined way, as to type and even stage of disease, dose, route of administration, and other characteristics, health insurers and managed care companies have found an opportunity to restrict patient access to new therapies.

At the very least, 50% of all cancer chemotherapy involves the use of drugs used in ways other than that for which they are approved. That is called "off-label" use. Until the present Commissioner undermined the credibility of his own agency, it participated in a "gentlemen's agreement" with the medical establishment about the validity and even

importance of off-label use in providing advances in treatment for people with cancer.

But those who would improve their profits at the expense of people's lives argue that they should not pay for off-label use, because if the FDA doesn't approve a use, it couldn't be effective, a kind of circular reasoning.

The self-serving hypocrisy of this position need not be underscored: it's apparent enough. But the problem remains. At its core is the nature of the approval designation. There are many other reasons, but under the constraint of time I can only strongly suggest that the FDA must approved drugs "for the management of cancer." Period.

There is another element of FDA thinking that irresponsibly and inhumanely violates patient needs and rights:

FDA operates on a "breakthrough" assumption: that when a drug is available to treat one type of cancer, any subsequent drugs for the same condition are not as urgently needed. This may be true for other diseases, in which one drug (and I am thinking of countless instances, such as Betaseron for MS, the drug for Tourette's syndrome, and such), where a "one-drug-fits-all" standard applies. That is not true in cancer, for two reasons:

1/ There are few certainties about cancer; how any patient responds to treatment is highly individual. No doctor can predict how anyone will respond to any drug or regimen. A range of drugs is needed to accommodate the variety of human responses.

2/ With time, people can become resistant to a drug. New drugs are needed if the patient is to continue to fight the disease.

The need for more drugs to be approved more quickly does not change when one drug is already out there. The FDA risks my life-- and yours-- in its assumptions.

Fifth, the FDA cannot operate in secrecy, because that's where its power comes from. **If an Advisory Committee rejects a drug, subsequent hearings must be public --and must go to a higher court.**

The history of the FDA is replete with wasted time, groundless questions, go-slow procedures, and political maneuvering. I would cite the approval of Gancyclovir as the quintessential example of time wasted, lives wasted. *The FDA has no sense of the urgency of people who need drugs to treat serious diseases.*

Mr. McINTOSH. Our next scheduled witness is Faith Samowitz, and her son, David, is here.

Faith, if you would like to start off?

STATEMENTS OF KIYOSHI KUROMIYA, DIRECTOR AND EDITOR, CRITICAL PATH AIDS PROJECT; FAITH SAMOWITZ, CITIZEN WITNESS; DAVID SAMOWITZ, CITIZEN WITNESS; AND MARIAH GLADIS, CITIZEN WITNESS

Ms. SAMOWITZ. Mr. Chairman and members of the committee, my name is Faith Samowitz, and with me today is my son, David. David and I want to thank you for this opportunity to talk directly to lawmakers about the effects of Government regulations on our lives.

David has epilepsy. When he was about 9 years old, he was first diagnosed with a seizure disorder, and then it was labeled epilepsy. We do not know what caused David's epilepsy. There are several possible causes for this order, including brain injuries, metabolic disorders and infections.

Epilepsy is a neurological disorder affecting some 4,000,000 Americans with about 100,000 new cases reported each year. The disorder is marked by recurring seizures. David has grand mal and complex partial seizures.

In 1987, after we had exhausted all medications and combinations of medications available in the United States, David's neurologist, Dr. Stanley Resor, suggested we try to some medications that were having some success in England, but were not available here. We did that, and now David is taking four medications. Until recently, all four were imported from England. Now two have become available in the United States.

With these medications, David's seizures are not too severe, but obtaining these medications has been a major problem. To get the medication, David obtains a prescription from his neurologist, and we send it to a London pharmacy that specializes in filling prescriptions for people from the United States. The pharmacy must then obtain a prescription from a local doctor, which is another expense.

The drug is shipped, and U.S. Customs must clear it. Then it goes to our local post office, which notifies us to pick it up. If all goes smoothly, we can get the drug in about 2 weeks, but life becomes very stressful. You hold your breath, you bite your nails, and you count pills the whole time because David cannot do without these medicines.

In 1991, U.S. Customs seized and burned a shipment of ours without even notifying us. We only found out about it after we wrote to the London pharmacy that we had not received the shipment. The pharmacy put a tracer on it and was notified by British postal authorities that the shipment had been seized by U.S. Customs as an illegal substance, an opiate.

The drug, Mogadan, is definitely not an opiate, and FDA regulations clearly state that patients with a physician's prescription should be able to import such drugs for their personal use.

Senator D'Amato kindly intervened on our behalf, and after about a year and many exchanges of letters, we were reimbursed

by the Customs agency under the Federal Tort Claims Act in the amount of \$209.65.

Since 1991, our shipments have not been seized, but we still must pay import duties on these medicines. It strikes me as wrong that the Government is taxing what is really a necessity to David's physical well being. This is not a luxury.

David and I are fortunate in several ways. We are fortunate to have Dr. Stanley Resor of Columbia-Presbyterian Hospital as David's neurologist. He is a renown authority on epilepsy. As a teacher in the New York City public school system, I am fortunate that my union's health plan reimburses me for the cost of these drugs, minus a \$5 deductible. Otherwise, Lamictal alone would have cost about \$6,000 last year. That is only for one medication.

Many people cannot get the drugs they need since most insurance plans do not cover drugs that are not available in the United States because they are not approved by the FDA. It is important to note that as the dollar suffers, so does the patient who buys medication abroad.

I believe that once medicines are approved in Europe or elsewhere and there have been sufficient trials and the medicines have been found somewhat successful, we should either rely on the foreign testing or work jointly with the other countries in order to have the drugs approved in a quicker fashion in the United States.

Compared to other countries, we seem to take forever to get drugs on the market. For example, one of the drugs David needs, Lamictal, was only approved here in December 1994. In December 1993, Dr. Resor told me it was going to be available, but it was not.

I would just like to have you consider proposing the changes in the drug approval process and to take into consideration families that are less fortunate than I am.

Thank you very much for listening.

[The prepared statement of Ms. Samowitz follows:]

DRAFT

TESTIMONY OF MRS. FAITH SAMOWITZ
June 9, 1995

Mr. Chairman and Members of the Committee,

My name is Faith Samowitz, and here with me today is my son, David. David and I want to thank you for this opportunity to talk directly to lawmakers about the effects of government regulation on our lives.

David has epilepsy. When he was about 9 years old, he would sometimes say, "I have the spots," or "I have the flicks." I thought he was just a very imaginative child until, one day, he told me he couldn't see. He walked around like a blind person, and I noticed that his pupils were dilated. I immediately took him to a neurologist, who diagnosed a seizure disorder and, finally, epilepsy.

We don't know what caused David's epilepsy. There are several possible causes of this disorder -- including brain injuries, metabolic disorders, and infections. Epilepsy is a neurological disorder affecting some four million Americans. with about 100,000 new cases reported each year. The disorder is marked by recurring seizures.

There are different types of seizures. David has experienced Grand Mal and Complex Partial seizures. In 1987, after we had exhausted all medications and combinations of medications available in the U.S., David's neurologist, Dr. Stanley Resor suggested we try some medications that were having some success in England but were not available here. Now that David is taking these four medications, his seizures are not so

severe. But obtaining these medications has been a major problem.

To get these medicines, David obtains a prescription from his neurologist, and we send it to a London pharmacy that specializes in filling prescriptions for people from the U.S. The pharmacy must then obtain a prescription from a local doctor (another expense). The drug is shipped, and U.S. Customs must clear it. Then it goes to our local post office, which notifies us to pick it up.

If all goes smoothly, we can get the drug in about two weeks. But life becomes very stressful. You hold your breath, you bite your nails, and you count pills the whole time, because David cannot do without these medicines.

In 1991, U.S. Customs seized and burned a shipment of ours without even notifying us. We only found out after we wrote to the London pharmacy that we had not received the shipment. The pharmacy put a tracer on it and was notified by British postal authorities that the shipment had been seized by U.S. customs as an illegal substance (opium). The drug, mogadan, is definitely not an opiate, and FDA regulations clearly state that patients, with a physician's prescription, should be able to import such drugs for their personal use. Senator D'Amato kindly intervened on our behalf and, after about a year and many exchanges of letters, the government reimbursed us for the \$209.65 cost of the medication under the Federal Tort Claims Act.

Since 1991, our shipments have not been seized, but we still

must pay import duties on these medicines. It strikes me as wrong that the government is taxing what is really a necessity to David's physical well-being. This is not a luxury.

David and I are fortunate in several ways. We are fortunate to have Dr. Stanley Resor of Columbia-Presbyterian Hospital as David's neurologist. He is a renowned authority on epilepsy. As a teacher in the New York City public school system, I am fortunate that my union's health plan reimburses me for the cost of these drugs, minus a \$5 co-payment. Otherwise, Lamictal alone would have cost about \$6,000 per year. Many people cannot get the drugs they need since most insurance plans do not cover drugs that aren't available in the U.S. because they aren't approved by the FDA. It is important to note that as the dollar suffers, so does the patient who buys medicines abroad.

I believe that once medicines are approved in Europe and there have been sufficient trials and the medicines have been found somewhat successful, we should either rely on the foreign testing or work jointly with the other countries in order to have the drugs approved in a quicker fashion in the U.S. Compared to other countries, we seem to take forever to get drugs on the market. For example, one of the drugs David needs -- Lamictal -- was only approved here in December 1994, after almost three years of review by the FDA. It was already available in more than 40 other countries and is available over the counter in Mexico. Another drug David needs, Sabril, is still waiting for FDA approval but has been available in England since 1989 and is also

on the market in six other industrialized countries.

I hope that as you consider proposals to change the drug approval process, you will consider the needs of families like ours and the needs of less fortunate families whose insurance plans do not cover drugs from overseas. I am sure that if you had someone close to you who suffered because of government regulations, you would want to change them. That is why I am sharing this story with you. Thank you very much for listening.

Mr. McINTOSH. Thank you very much. I appreciate your coming today.

David, do you also have a statement? We appreciate your coming.

Mr. SAMOWITZ. Good morning, Mr. Chairman, members of the committee. My name is David Samowitz. I am 24 years old, and as my mother has told you, I was diagnosed with epilepsy with I was 9.

As you may know, many famous people and high achievers also had epilepsy, including Napoleon Bonaparte, Julius Caesar, George Frederick Handel, Socrates, St. Paul and Peter Tchaikovsky. I am optimistic that with access to the medicines I need, I can also achieve something in my life.

I am now in a training program to be a mail clerk, but I am most interested in electronics. I enjoy filming with a camcorder, and people have said I do a very professional job.

My condition has improved with the medicines I am taking, but it bothers me that products are available in England and other countries before they are put on the market here.

Mogadan, generic name Nitrospan, has also been available in England about 5 years. I have heard that it may never be approved in the United States. I have been using Mogadan for approximately 4½ to 5 years.

If countries can work together to fight wars or to help other countries, why can they not work together on helping people get the medicines they need? The current situation is very hard on people like me. I hope you will do something to change it.

Thank you very much for your attention.

[The prepared statement of Mr. Samowitz follows:]

DRAFT

STATEMENT OF DAVID SAMOWITZ
June 9, 1995

Good morning,

My name is David Samowitz. I am 24 years old, and as my mother has told you, I was diagnosed with epilepsy when I was 9.

As you may know, many famous people and high achievers also had epilepsy, including Napoleon Bonaparte, Julius Caesar, George Frederick Handel, Socrates, St. Paul, and Peter Tchaikovsky. I am optimistic that, with access to the medicines I need, I can also achieve something in my life. I am now in a training program to be a mail clerk, but I am most interested in electronics. I enjoy filming with a Camcorder, and people have said I do a very professional job.

My condition has improved with the medicines I am taking, but it bothers me that products are available in England and other countries before they are put on the market here. If countries can work together to fight wars or to help other countries, why can't they work together on helping people get the medications they need?

The current situation is very hard on people like me. I hope you will do something to change it.

Thank you very much.

Mr. MCINTOSH. Thank you very much, David. I think your statement of aspiration is one we should all strive for in working together for that purpose.

Our next witness is Ms. Mariah Gladis. Mariah, we appreciate your coming today. Please share with us your testimony.

Ms. GLADIS. Good morning. Let me begin my story here. I am not deaf. I have ALS or Lou Gehrig's disease. I am a resident of Malvern, PA. I am a mom with two wonderful sons, ages 11 and 19. I am the wife of Ronn, here in the room. I am the founder and director of the Pennsylvania Gestalt Center for over 20 years.

I would like to thank you, Congressman Fox, and other members of this committee.

I have felt some confusion about the direction of the FDA. Dr. Kessler, Commissioner of the FDA, said in a 1994 edition of *Newsday*, "When people are suffering and dying from a devastating disease, we cannot wait for all the evidence to come in—for all the i's to be dotted and all the t's crossed. We must be prepared to accept greater risks from a drug when greater benefits are possible." If the FDA adhered to this, I would not be here today.

Later in 1994, he said, "There is a clash between the right of the individual—to get any drug—and the duty of the Government to prevent harm."

We certainly believe that safety is important, but we wonder what are we being protected from and prevented from?

Dr. Kessler's last statement tells me that the FDA may be missing a central point of battling a terminal illness. Taking control of one's illness is incredibly important. Making a drug available or increasing the options to obtain a new therapy or even providing new educational materials is so critical because it yields hope.

Hope is life giving in and of itself. Hope is based partly on the knowledge of your disease and the support that you receive from the healthcare system.

Let me tell you about me. On June 30, 1981, I received a terminal diagnosis and a marriage proposal. Eventually I was first diagnosed with a brain tumor and later on with ALS. I was given a 10-percent chance of surviving a half a year to 2 years.

I searched for public information. There was very, very little. Doctors did not know what caused this, nor did they have any drugs or treatment at all. Ronn and I knew that we were faced with moving toward life or death. Had I listened, I would not be here today.

In many respects, we have had to create our own hope. I began seeing a nutritionist and started an aggressive antioxidants program with exercise.

Let me state the key issues that can help save or at least maximize time for ALS patients. Start combination drug trials now. Improve the expanded access program. People with life threatening illness want access and the choice to take experimental drugs when they have reached or completed phase III. How can the FDA expedite and facilitate this access? What are they going to do to streamline this process to help save lives?

Breakdown barriers to experimental drugs. Avoid the use of placebos in future trials. The ALS Association has stated that, "Like cancer, once a drug is identified as being effective in treating a par-

ticular disease, researchers commonly design future trials that compare the reference drug versus a new drug or a combination of the reference and new drug." Once we have a drug that works in ALS, why should patients have to take placebo?

Since 1992, there is a new drug that is more effective in treating ALS. I tried to get that drug, but because of FDA regulations I was not able to get it because they knew that it would not help in 1992. I had many friends with ALS who were still alive in 1992. Now it is 1995, and we need these drugs available.

I urge them to hurry and make it available. I am running out of time. I thank you, and I know that my husband and sons thank you. Let us make this opportunity available now.

[The prepared statement of Ms. Gladis follows:]

TESTIMONY OF MARIAH GLADIS
U.S. HOUSE GOVERNMENT REFORM & OVERSIGHT COMMITTEE
June 9, 1995 -- Norristown, PA

Good morning. I am Mariah Gladis, a resident of Malvern, Pennsylvania. I am a mother of two handsome boys....the wife of Ronn Gladis for 14 years and is the Founder and Director of the Pennsylvania Gestalt Center for over 20 years. I also have a terminal illness called amyotrophic lateral sclerosis, which is better known as ALS or Lou Gehrig's disease.

Today, I would like to thank you -- Congressman Jon Fox -- and the other members of this Congressional Committee for the opportunity to focus on a common goal.....to speed up the FDA approval process for life-extending and life-saving drugs. We all hope that through your efforts and others like this, that future meetings won't be needed.

I have certainly felt some confusion about the direction of the FDA, which is perhaps best illustrated by two separate quotes from Dr. David Kessler, Commissioner of the FDA. Dr. Kessler stated in the March 1, 1994 edition of New York Newsday that:

"When people are suffering and dying from a devastating disease, we can not wait for all the evidence to come in -- for all the i's to be dotted and all the t's crossed. We must be prepared to accept greater risks from a drug when greater benefits are possible."

Congressman Fox and Committee members, we clearly agree with this statement. If the FDA adhered to this philosophy, I would be up here providing a testimonial to their work.

However, we often see contradictory statements and actions that leave us wondering what are their real goals? An example of this type of conflicting statement can be found in the January 30, 1995 issue of Business Week, where Dr. Kessler also stated that:

"There is a clash between the right of the individual (to get any drug) and the duty of government to prevent harm."

Congressmen, we certainly believe that safety is important, but we often wonder what we are being protected from! What is the harm that we are being prevented from?

Dr. Kessler's last statement tells me that FDA may be missing a central point of battling a terminal illness. Taking control of one's illness is incredibly important. Making a drug available or increasing the options to obtain a new therapy or even providing new educational materials is so critical because it yields hope which is life giving in and of itself. We shouldn't worry about false hope because hope is often the only life giving force that we have. We need an FDA that places less emphasis on preventing harm and more emphasis on making changes that provide a way to rally around a drug or new trial to generate even more health and hope.

Hope is based, at least partly, on knowledge of your disease and the support you receive from the healthcare system. I believe that the more options people with ALS have for treatment, the more options they will also have for education. Why is this so important you may ask? I would like to explain by discussing my personal bout with ALS.

In 1981, I was first diagnosed with a brain tumor. Several months later, I was diagnosed with ALS and was told matter-of-factly that I had a 10 percent chance to live six months to two years. Yes...that's right...a 10 percent chance to live another six months. Faced with this diagnosis, I searched for public information and found nothing that provided a different perspective -- nothing gave any hope at all.

With physicians telling me there was nothing to offer and no reason to plan for the future, we did the unexpected -- Ronn and I got married and started a family because we knew then that we had a chance to move toward death or toward life with all the hope we could muster.

In some respects, we have created our own hope in the absence of any positive news. I began seeing a nutritionist and started an aggressive anti-oxidants program. Diet and exercise became tangible ways to "do something". And, of course, with two young boys, our family activities are filled with athletic activities and other family-oriented moments that only increase my appreciation of time.

It has been said before that "To love life is to love time". This brings me back to the action I hope this Committee will take. Perhaps it is easiest if I state the key issues that can help save or at least maximize time for ALS patients.

1) **START COMBINATION DRUG TRIALS NOW** -- The question is under what circumstances will the FDA accept the submission of a protocol for a clinical trial utilizing two experimental drugs, both having completed the safety trial phase? And, if the FDA won't consider this scenario, they need to explain their rationale and what it will take to change their position.

2) **IMPROVE THE EXPANDED ACCESS PROCESS** -- People with life-threatening illness want expanded access and the choice to take experimental drugs when they have reached or completed Phase III. How can FDA expedite and facilitate this access? What is the FDA going to do to streamline this process to help potentially save lives?

3) **BREAK DOWN BARRIERS TO EXPERIMENTAL DRUGS** -- Patients are willing to pay for experimental drugs, either personally or via health insurance. In the case of ALS, we don't have any approved drugs on the market yet. To encourage compassionate access for new drugs, drug companies should be able to commercialize or gain a profit from the sale of these drugs.

4) AVOID THE USE OF PLACEBO IN FUTURE TRIALS – The ALS Association has stated that "like cancer, once a drug is identified as being effective in treating a particular disease (regardless of how minimal), researchers commonly design future trials that compare the reference drug versus a new drug or a combination of the reference and new drug." Basically, once we have a drug that works in ALS, why should patients have to take a placebo? My next statement is about such a drug.

5) APPROVE NEW DRUGS AS FAST AS POSSIBLE – I have been out to talk to the people at Rhone-Poulenc Rorer in Collegeville, Pennsylvania and I've been following their drug development program for Rilutek since 1992. I tried to get it then, but the FDA system didn't allow for patients to find ways to gain access to it beyond the Phase III trial. In the meantime, the existing trials demonstrated that Rilutek is the first drug to prolong survival of people with ALS. Today, I know the FDA is reviewing a treatment protocol that will allow for access to this drug before approval. And, I know the company is planning to provide FDA with the New Drug Application this July. But the real question is how much longer do I have to wait to get the drug?

I can't afford to wait around for the conclusion of endless drug trials and FDA review. My husband Ronn, myself and my sons, Luke and Cole, simply don't have time. I didn't have the speech or physical impediments that I have now in 1992. Many of my friends with ALS were still alive in 1992. Now, it's 1995 and we want, we need the opportunity to get this drug.

Last week, I lost the use of the fourth finger on my left hand. Access to a drug like this (Rilutek) may have prevented or delayed many of my losses in my case. Others have lost more than a finger, others have already lost their lives.

Thank you Congressman Fox and fellow members of the Committee.

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Mr. MCINTOSH. Thank you for coming here. You are a very brave woman, and we all really appreciate you testifying here today.

We will hear later from the FDA, and we will put your questions to them on how we can speed that up.

Ms. GLADIS. All right.

Mr. MCINTOSH. Thank you very, very much.

Ms. GLADIS. Thank you.

Mr. MCINTOSH. Our next witness is an advocate for AIDS patients, Mr. Kiyoshi Kuromiya. Thank you, Mr. Kuromiya, for coming.

Mr. KUROMIYA. Thank you, Chairman McIntosh and panel members for this opportunity to testify for myself and on behalf of my community.

As a Philadelphian with full-blown AIDS and a vocal advocate for my community, I must preface my remarks by saying that I appreciate the fact that the FDA over the last 5 years has implemented accelerated approval programs for AIDS drugs under community and activist pressure.

Further, I want to say that I do not support congressional micro-management of regulatory agencies and do not believe Congress should set the scientific agenda for this country, but we have come to a time when it may be possible to improve an agency, the FDA, which in some regards has lost sight of its mandate.

My concern as a person with AIDS and a treatment activist who has worked as a community representative since 1991 in the ACTG and CPCRA clinical trials programs of the NIH, my concern is that conspicuously absent from Kessler's recent presentation to the Senate Labor and Human Resources Committee were any new effort to speed approval of drugs for AIDS.

Since the drive for faster drug approval was spearheaded by AIDS activists and one of the areas where the FDA has made progress is in accelerated approval of drugs for persons with AIDS, we were surprised and disturbed that Kessler neglected to highlight this area in his proposed FDA reforms.

Perhaps a clue to Kessler's snub of AIDS drugs can be found in his article in the March, 1995, Scientific American in which he claimed ACT UP members have undergone a change of heart, and now AIDS activists want the FDA to slow down.

This is not true. Kessler failed to mention in his article that the activists to whom he referred were not really ACT UP members. They were from Treatment Action Group, a group that broke from ACT UP a couple years ago primarily because of disagreement over the pace of drug approval.

During 2 days of hearings that took place last September, he listened to scores of angry persons with AIDS and treatment activists, including myself, representing 100 AIDS organizations demanding that he approve AIDS drugs faster, not slower. Kessler's cynical and even dishonest manipulation of the community's position in this matter shows a real contempt for people with AIDS.

Many of us who have HIV infection or AIDS owe our present good health to the drugs we get through such innovative programs as expanded access, treatment IND's, accelerated approval, compassionate use and parallel track.

We need even more such programs which get experimental drugs of potential treatment benefit to the people who have urgent need for them and get them to these persons fast once safety has been established. As persons with AIDS, we are tired of waiting endlessly for drugs of proven safety to make their way through the approval process.

We have fears regarding the FDA reforms in the bill that Democrat Ron Wyden of Oregon has promised to introduce before Memorial Day. The Republican bill, we are assured, will follow in a few days. Both bills are expected to deregulate phase I clinical trials, but the Democratic version will almost certainly not codify accelerated approval. Because of these moves, we are going to wake up and find the AIDS drug pipeline is empty.

During the 1950's, drug approval was a relatively quick and simple process in the United States, like it is today in Europe. Then came Thalidomide. Several hundred babies were born with horrible defects after European regulators approved the drug for morning sickness without realizing it could affect the fetus.

Capitalizing in the tragedy, Congress expanded FDA's powers and altered its priorities. These overly cautious policies have hindered drug approval ever since.

In November 1994, the experimental AIDS drug, 3TC, then in phase III testing, was shown to significantly increase and extend the efficacy of AZT, the standard therapy, when combined with it. The 3TC/AZT combination cannot be approved until the spring of 1996. The FDA wants another level of clinical end point studies.

Meanwhile, more than 100,000 AIDS patients will remain on the far less effective AZT monotherapy, a drug which is shown to lose effectiveness after a year or so of use. Persons who are not among the lucky 17,000 who have gotten on a compassionate use program or the additional thousands on the waiting list are out of luck.

Only persons with a CD4 count of below 100, in other words, with very advanced AIDS, qualify; not to get the drug, but to be put on the waiting list. I have a CD4 count that was 10 in December. It is much higher now by virtue of my access to 3TC. I must admit that I was unable to get the drug through the usual FDA channels and was forced to look to community resources. Otherwise I potentially face earlier disease progress and death. We need to speed up the process, not slow it down.

Another example. A number of AIDS treatment activists and former clinical trial participants from Philadelphia have been fighting for 5 years now to get approval for expanded trials of Jonas Salk's HIV-1 immugen, a therapeutic vaccine for persons already infected with HIV, a product which has been in human trial since 1988 with a perfect safety record.

It was not until January that tentative approval for phase III trials was granted for a multicenter study of several thousand individuals. Many of them signed our petitions and have been waiting over 3 years.

Because of the costly and slow process, many small biotech companies, including Immune Response Corp., the manufacturer of the Salk immugen, are nearly bankrupt by the time they get to the point of approval, slowing down the process even more from the

point of view of persons with AIDS who feel lifesaving drugs are being kept from them because of bureaucratic red tape.

Although I will not go into detail in this area, the FDA restricts a flow of information on drugs. It penalizes drug manufacturers for third party reports of off label uses of drugs. PWA's, in other words, people with AIDS, must resort to getting Algendazole for off label use of treating microsporidiosis through community buyers clubs, from other countries such as Mexico, or use the veterinary version of this drug. Why go to such lengths? Because diarrhea from GI tract microsporidiosis, if uncontrolled in a PWA, can lead to death.

Medicinal marijuana is a whole other issue which I will not go into detail today. It was approved for use by persons with glaucoma and multiple sclerosis and AIDS in the 1980's and then in 1988 suddenly banned by President Bush.

Persons with AIDS who get nausea from the dozens of medications they take each day, and I take about 25 or 30 separate pills per day, use it to control nausea.

Marijuana is also effective for persons with AIDS and wasting syndrome. I have lost 30 pounds of weight in the last 12 months, but I have stabilized my weight loss through control of my nausea and appetite loss with marijuana. The reason my weight loss has been stabilized for the past 6 months is because I have found access to marijuana through underground sources.

Because of the politically charged nature of this issue, Phil Lee of HHS, Al Leshner of NIDA and David Kessler of the FDA have independently not only denied me access to an important herbal medicine which has been used safely world around for its medicinal properties for 5,000 years.

There are people going blind from glaucoma or suffering needlessly from AIDS related wasting syndrome, and yet marijuana cannot even be studied in a clinical trial, such as the one proposed by Donald Abrams of San Francisco General Hospital, which compared smoked marijuana and Marinol, a less effective medication containing marijuana's active ingredient, THC.

Marinol is approved for use in the United States and recently approved for coverage through AIDS drug assistance programs in the State of Pennsylvania.

All this, when according to a recent survey over 80 percent of the American public supports providing limited access to marijuana for its proven medicinal value.

The total cost of FDA's review and approval procedures has steadily risen and risen rapidly since 1962. During that time, neither Congress nor the FDA has ever conducted a thorough, reputable study of FDA performance that justifies these rising costs either in terms of lives saved, improved medical practice or identifiable benefits to the U.S. economy.

Finally, as a person with AIDS, I find that my efforts to get promising new treatments to persons who need them the most always leads to the FDA, where the process often comes to a standstill. Accelerated approval programs need to be expanded to the area of biotech products without setting a higher standard for biologicals.

We feel reforms of the FDA are needed, but we must not abandon the hard fought for improvements in the AIDS drug approval process that have been made under pressure from the AIDS community. I owe my life and good health to these programs.

If the FDA turns its back on persons with AIDS the way much of the rest of the Federal bureaucracy has, we will suffer the consequences of the human as well as monetary expense of such short-sighted planning. Persons with AIDS will be hospitalized sooner and kept there longer.

Our goal is an improved FDA that will expedite approval of drugs that will keep persons like myself, who has never been in the hospital for HIV related infections, out of the hospital for many more years of productive life. We can do it with your help.

Thank you for listening.

[The prepared statement of Mr. Kuromiya follows:]



FDA Regulatory Reforms

Statement of Kiyoshi Kuromiya

Director/Editor

Critical Path AIDS Project

June 9, 1995, Norristown, Pennsylvania

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As a person with AIDS and a vocal advocate for my community, I must preface my remarks by saying that I appreciate the fact that the FDA over the last five years has implemented accelerated approval programs for AIDS drugs under community and activist pressure. And further, I want to say that I do not support Congressional micromanagement of regulatory agencies, and do not believe Congress should set the scientific agenda for this country. But, we have come to a time when it may be possible to improve an agency--the FDA--which in some regards has lost sight of its mission.

Last month at the GOP summit legislation to reform the FDA was presumably one of the unannounced topics of discussion facing lawmakers. This legislation seems even more certain since FDA Commissioner David Kessler gave the Senate Labor and Human Resources Committee an outline of the Clinton Administration's proposed FDA reforms.

My concern as a person with AIDS and a treatment activist who has worked as a community representative since 1991 in the AIDS Clinical Trials Group program of the NIH is that conspicuously absent from Kessler's presentation were any new efforts to speed approval of drugs for AIDS. Since the drive for faster drug approval was spearheaded by AIDS activists and one of the areas where the FDA has made progress is in accelerated

approval of drugs for persons with AIDS, we were surprised and disturbed that Kessler neglected to highlight this area in his proposed FDA reforms. Perhaps a clue to Kessler's snub of AIDS drugs can be found in his article for the March 1985 *Scientific American* in which he claimed ACT UP members have undergone a change of heart and now prefer the slow progression of drugs through the FDA to accelerated approval. According to one pharmaceutical company lobbyist, not only the FDA director but "Kessler's people" are all over Washington telling everyone that AIDS activists want the FDA to slow down.

Kessler failed to mention in his article that the activists to whom he referred were not really ACT UP members, they were from Treatment Action Group (TAG), a group that broke from ACT UP a couple of years ago, primarily because of disagreement over the pace of drug approval. Kessler also failed to mention the firestorm of opposition in both ACT UP and within the AIDS patient community, sparked by TAG's asking him to slow down. Over 100 AIDS organizations, including ACT UP groups from many cities, signed a consensus letter supporting faster drug approval. During two days of hearings that took place last September, he listened to scores of angry persons with AIDS (PWAs) and treatment activists from around the country (including myself) demanding that he approve AIDS drugs *faster*, not *slower*.

Kessler was at that meeting, listening to David Barr and other TAG members, change their position and join the majority to say that they favored accelerated approval. Yes, he reiterated that meeting at a March 28 Congressional hearing, and Jim Driscoll quotes him, in a recent *Bay Area Reporter* article: "I was at a fascinating meeting, and it was a real eye-opener. . . . It was with AIDS activists . . . the same activists who were scaling the walls of Parklawn a number of years ago, saying 'FDA speed up the drug approval process.' They came in and said to me, 'Commissioner, you are approving drugs too quickly. We don't know how to take them, when to take them, in what dose to take them. We need to know whether these drugs work.'"

Kessler's cynical, even dishonest, manipulation of the community's position shows a real contempt for people with AIDS. One drug company lobbyist told Jim Driscoll that this new perception--that AIDS activists no longer want FDA to approve AIDS drugs faster will hurt efforts to get life-saving drugs to persons like me as fast as is safely possible. He predicted that companies will stop investing in AIDS if they think the FDA will slow down on approving new AIDS drugs, and Congress may write an FDA reform bill that speeds everything except AIDS drugs.

Many of us who have HIV infection or AIDS owe our present good health to the drugs which through such innovative programs as expanded access, treatment INDs, accelerated approval, compassionate use, and parallel track,. We need even more such programs which get experimental drugs of potential treatment benefit to the people who have urgent need for them... and get them to these persons fast. once safety has been established. As persons with AIDS, we are tired of waiting endlessly for drugs of proven safety to make their way through the approval process. This is an area we feel David Kessler has made some progress and yet we have the feeling that all our gains will soon be lost and the FDA will loose sight of its mission as Kessler tries to go back on the reforms that have expedited the process of getting drugs to the people who need them, once toxicities are known and safety issues are resolved.

We have fears regarding the FDA reforms in the bill that Democrat Ron Wyden of Oregon has promised to introduce before Memorial Day. And the Republican bill, we are assured will follow in a few days. Both bills are expected to deregulate Phase I clinical trials, but the Democratic version will almost certainly not codify accelerated approval. Because of these moves, we are going to wake up and find the AIDS drug pipeline is empty.

During the 1950s drug approval was a relatively quick and simple process in the US, like it is today in Europe. Then came thalidomide. Several hundred babies were born with horrible defects after European regulators approved the drug for morning sickness without realizing it could affect the fetus. Capitalizing on the tragedy, liberals in Congress expanded the FDA's powers and altered its priorities. These policies have hindered drug approval ever since. A survey of 137 new drugs approved by the FDA between 1986 and 1991 found that on the average the same products were approved by European regulatory agencies 4.1 years faster than by the FDA. Investigational new drug (IND) application filing to new drug application (NDA) submission items averaged 2.5 years for the 1960s, 4.4 years for the 1970s, 5.5 years for the 1980s, and 6.1 years for the 1990s. To give an example of how this may indirectly harm many persons in this country, an application for approval of a vaccine for Hepatitis A was filed with the FDA 32 months ago. Though FDA has yet to reach a decision, it is already on the market in 40 other countries. Through 1992, 92 monoclonal antibodies had been approved in Europe, compared to only 8 in the United States. 42 new vaccines had been approved in Europe against 8 in the United States. 64 recombinant DNA products were approved in Europe against 21 in the United States.

In November 1994, the experimental AIDS drug 3TC, then in Phase III testing, was shown to significantly increase and extend the efficacy of AZT, the standard therapy, when combined with it. The 3TC/AZT combination cannot be approved until the spring of 1996. The FDA wants another level of clinical endpoint studies. Meanwhile, more than 100,000 AIDS patients will remain on the far less effective AZT monotherapy, a drug which has been shown to lose effectiveness after a year or so of use. Persons who are not among the lucky 17,000 who have gotten on a compassionate use program or additional thousands on the waiting list, are out of luck. Only persons with a CD4 count of below 100. In other words with very advanced AIDS, qualify, not to get the drug but to be put on a waiting list. I have a CD4 count that was 10 in December and is much higher now by virtue of my access to 3TC. But I must admit, that I was unable to get the drug through the usual FDA channels and was forced to look to community resources. Otherwise I faced potentially earlier disease progress and death. We need to speed up the process, not slow it down.

Today, nearly all major US drug companies run most of, if not all, their Phase I clinical trials in Europe. Since the FDA failed to implement Competitiveness Council reform of Phase I, early clinical research fled the country to avoid the US regulatory burden. FDA's failure to reform Phase I disadvantages small American biotech companies who lack European research centers. For example, a number of AIDS treatment activists and former clinical trial participants from Philadelphia have been fighting for 6 years now to get approval for expanded trials of Jonas Salk's HIV-1 Immunogen (a therapeutic vaccine for persons already infected with HIV), a product which has been in human trials since 1988 with a perfect safety record. It was not until January that tentative approval for Phase III trials was granted for a multicenter study of several thousand individuals, many of them signed our petitions and have been waiting for over three years. And because of the costly and slow process, many small biotech companies including Immune Response Corporation (the manufacturer of the Salk Immunogen) are nearly bankrupt by the time they get to the point of approval, slowing down the process even more from the point of view of PWAs who feel life-saving drugs are being kept from them because of bureaucratic red tape.

As compared to Europe, the FDA demands excessive and expensive (in time and resources) caution in early clinical research. In Phase I, the FDA commonly demands decreased dosages, lengthy observation periods, and discussions at each stage. The FDA, often requires raw data where European agencies accept summaries of data in New Drug Applications (NDAs), so US applications from biotech companies can sometimes amount to

thousands of pages as compared to a few dozen pages for the same drug in order to fulfill European requirements.

Although, I will not go into detail in this area, the FDA restricts the flow of information on drugs. It also requires on off label use and promotion, an approach which often backfires and harms the very persons it is intended to protect: children with rarer forms of cancer to give one example and off-label uses of drugs like albendazole for treatment of persons with AIDS who are fighting microsporidiosis an intestinal tract infection for which there are no good treatments. PWAs must resort to getting albendazole for this off-label use through community "buyers' clubs," from other countries such as Mexico, or the veterinary version of the drug. Why go to such lengths? Because diarrhea from microsporidiosis if uncontrolled in a PWA can lead to death.

Medicinal marijuana is a whole other issue which I will not go into detail today. It was approved for use by persons with glaucoma and multiple sclerosis and AIDS in the 80s and then in 1988 suddenly banned by President Bush. Persons with AIDS who get nausea from the dozens of medications they take each day use it to control nausea. Marijuana is also effective for persons with AIDS and wasting syndrome. I have lost 30 lbs. weight in the last 12 months but have stabilized my weight loss through control of my nausea and appetite loss with marijuana. The reason my weight loss has been stabilized for the past six months is because I have found access to marijuana through underground sources. Because of the politically charged issue, Phil Lee of HHS, Alan Leshner of NIDA, and David Kessler of the FDA have not only denied me access to an important herbal medicine which has been used world around for its medicinal properties for 5,000 years. There are people going blind from glaucoma or dying from AIDS-related wasting syndrome, and yet marijuana cannot even be studied in a clinical trial such as the one proposed by Donald Abrams of SFGH, which compares smoked marijuana and marinol, a less effective medication containing THC.

The total costs of FDA's review and approval procedures have risen steadily and rapidly since 1962. During that time neither Congress nor the FDA has ever conducted a thorough, reputable study of FDA performance that justifies these rising costs either in terms of lives saved, improved medical practice, or identifiable benefits to the US economy.

Finally, as a person with AIDS, I find that my efforts to get promising new treatments to persons who need them almost always leads to the FDA where the process often comes to a standstill. The situation for persons with AIDS has improved with the innovative programs

for accelerated approval, but these programs need to be expanded, not scrapped. For example, they need to be expanded to the area of biotech products, without setting a higher standard for biologicals. We feel reforms of the FDA are needed, but we must not scrap the hard-fought-for improvements in the AIDS drug approval process that have been made under pressure from the AIDS community. If the FDA turns its back on persons with AIDS the way much of the rest of the Federal bureaucracy has, we will suffer the consequences of the human as well as monetary expense of such short-sighted planning. Persons with AIDS will be hospitalized sooner and kept there longer.

Our goal is an improved FDA that will expedite approval of drugs that will keep persons like myself, who has never been in the hospital for HIV-related infections, out of the hospital for many more years of productive life. We can do it, with your help. Thank you for listening.

Mr. McINTOSH. Thank you very much, Mr. Kuromiya. We appreciate you coming forward and testifying today.

Now we move into a brief session on questions from the panelists. In order to save time for my colleagues, I will take your questions that you have for the agency and formulate them at one of the later parts of the panel.

Does anyone have any questions for this set of witnesses? Mr. Fox?

Mr. FOX. Yes. Kiyoshi, I will start with you. Do you feel that the problems that were brought on by Thalidomide have created a go slow attitude within the FDA?

Mr. KUROMIYA. Yes. I could go on to other areas where the FDA has looked away while 430,000 people died from cardiac and respiratory conditions related to smoking cigarettes. Over 40,000 die each year from secondary effects of cigarette smoking, more than die from AIDS each year. That is another area, though.

Mr. FOX. But there is an over reaction, as far as you are concerned?

Mr. KUROMIYA. There is an over reaction. I think we have become overly conscious or overly cautious in terms of protecting the public.

We know the entire Thalidomide story. Persons with AIDS are rapidly enrolling in clinical trials that use Thalidomide for ulcers and its antiviral. We are quite aware of the situation with fetuses, and protections are taken. Otherwise, Thalidomide is a relatively benign drug, even as compared to the approved drugs for persons with AIDS and approved drugs for chemotherapy, which are quite toxic.

Mr. FOX. All the members up here today are working on the legislation that you made reference to, which would be when filed the Life Extending/Lifesaving Drug Act of 1995. It occurs to me that your testimony is quite pointed, as were the other witnesses in this panel, regarding the importance of speeding up the process.

Do you think we should put time lines on it? From your perspective, what do you think the legislation should be or the corrections within the agency should be to speedup the process? Give us a specific guideline.

Mr. KUROMIYA. One area, for example, which the FDA really is not prepared to take on is biologicals. I think that there are some groundbreaking new developments in this area.

The FDA is using overly cautious procedures requiring extra levels of viral deactivation, for example, in the area of vaccines, therapeutic and preventive vaccines. We feel that this slows down the process and keeps potentially valuable drugs both from being tested and from moving through the drug approval process at a rapid pace.

Mr. FOX. I have no further questions, Mr. Chairman.

Mr. McINTOSH. Thank you, Mr. Fox.

Mr. Clinger?

Mr. CLINGER. I just would like to thank all of the witnesses for your very moving and compelling testimony. I think it has been enormously helpful I know to us because you have corroborated what I think we have all known, and that is that there is an unconscionable delay in making medicines available to you that could

be helpful. I think you have been very persuasive witnesses, and we thank you for your testimony.

Mr. MCINTOSH. Mr. Peterson, do you have any questions?

Mr. PETERSON. I want to also thank the panel, and hopefully we can put some of their questions to the agency. Thank you.

Mr. MCINTOSH. Mr. Fox indicated he has one further question.

Mr. FOX. Mr. Samowitz, your testimony was quite compelling, as were the others, especially with regard to the fact that you have to get your medicines from England. Are you still getting them from England as well?

Mr. SAMOWITZ. Yes.

Mr. FOX. They are not available in the United States?

Mr. SAMOWITZ. Correct.

Mr. FOX. What does it cost for you a year, if you know, approximately or a month?

Mr. SAMOWITZ. You would have to ask my mother. You will have to wait until she comes back.

Mr. FOX. Your mother is coming forward. Mrs. Samowitz, could you help illuminate us on the question of the cost?

Ms. SAMOWITZ. As I said, my union plan covers my medication, but the Lamictal, which until recently I was getting from England, would have cost roughly \$6,000 a year. It is a little over \$500 a month. That is just for the one medicine. One of the others is about \$500, but that lasts 3 months. Mogadan is about \$250. That lasts about—

Mr. FOX. And there were some months you did not get receipt of them?

Ms. SAMOWITZ. Pardon?

Mr. FOX. Did you ever have to go any time where you did not get them because of a delay in the mail?

Ms. SAMOWITZ. Dr. Resor has a list of patients, and when we are really running short we call. They will Express Mail it to us, and then when we get our shipment, we Express Mail it back.

Mr. FOX. As you expressed in your testimony and in your son's, I guess some people actually cannot afford it. They, of course, do not get it.

Ms. SAMOWITZ. They cannot even bother with it because of the enormous expense.

Mr. FOX. I thank you.

Mr. MCINTOSH. Thank you very much.

Mr. Tate?

Mr. TATE. I would like to followup with that as well, that whole issue. How do you come in contact or get the knowledge of these drugs in other countries? If they are not approved in the United States but you are allowed to do them through direct mail of some sort, how do you come in contact? Does your doctor suggest that you do this?

Ms. SAMOWITZ. My doctor, I guess through the journals and the research, is aware of all the drugs being tested in other countries. He has followed them and when they become available in the other countries.

If all else fails—I mean, he was just having no success with the medicines available. He would have four to five seizures a week. We are talking about grand mal. He just falls. I do not want to tell

you how many times I have gone to the emergency room, to the police station. I get calls from people in the street.

That is an unfortunate part that David has, but he has had a lot more success with the medicines from England.

Mr. TATE. Are you familiar, and I do not know if you mentioned it, with Colpizone?

Ms. SAMOWITZ. Yes.

Mr. TATE. Is it my understanding that their patent is about to expire in the United States. It is my understanding that there is no company that is willing to go through the FDA approval in the United States just because the expense is so much——

Ms. SAMOWITZ. Yes.

Mr. TATE [continuing]. That they are going to continue to have to get it overseas.

Ms. SAMOWITZ. Yes, I am familiar, and we still do get it.

Mr. TATE. I would also like to add that I just appreciate your openness and your willingness. I know it is difficult to talk about these issues, but I sure appreciate your honesty and your willingness to take the time to come here. It has really been moving testimony for me personally. I just want to say thank you.

Mr. MCINTOSH. Thank you very much, Mr. Tate.

Mr. Walker, do you have any questions?

Mr. WALKER. I have no questions, but I, too, want to thank the panel. I think it is very important from time to time to take what is essentially regulatory reform issues and put a human dimension on them.

What we have had here this morning is a very, very important human dimension to the decisionmaking that we are going to try to do.

Thank you very much for being here.

Mr. MCINTOSH. Thank you, Mr. Walker.

Thank you all very, very much for coming here. We all appreciate it. This will be enormously helpful to us, and we will take this information back with us. It will become part of the record and the process in Washington as to move to speedup this drug approval process.

We appreciate all of you coming. We may in fact from time to time be in touch with you as we get new information or have additional questions.

Thank you.

Let us move now to the second panel of today's schedule. This is a panel of representatives of several of the drug and pharmaceutical companies here in the district. We will hear from their experts on suggestions they have for speeding the drug approval process, which will be helpful to us as we go forward in this inquiry.

Let me say that this clock with the lights apparently is not working, so I have asked one of the staff members to hold up a little sign at 3 minutes and then at 5 minutes. We will try to keep the schedule going.

If you could all rise and please raise your right hand?

[Witnesses sworn.]

Mr. MCINTOSH. Let the record show the witnesses answered in the affirmative.

Our first witness is Dr. David Blois, who is vice president of worldwide regulatory affairs with Merck & Co.
Dr. Blois.

STATEMENTS OF DR. DAVID BLOIS, VICE PRESIDENT, WORLD-WIDE REGULATORY AFFAIRS, MERCK & CO.; ACCOMPANIED BY JAMES T. MOLT, VICE PRESIDENT, WORLDWIDE REGULATORY AFFAIRS, RHONE-POULENC RORER; ROBERT POWELL, VICE PRESIDENT AND DIRECTOR, REGULATORY AFFAIRS, SMITHKLINE BEECHAM PHARMACEUTICALS; BRUCE CARROLL, MANAGER, GOVERNMENT RELATIONS DIVISION, CENTOCOR, INC.; AND ROBERT H. LARKIN, DIRECTOR, REGISTRATION AND REGULATORY AFFAIRS, AGRICULTURAL CHEMICALS BUSINESS, ROHM AND HAAS CO.

Mr. BLOIS. Good morning Mr. Chairman and Congressman Fox and members of the committee.

As you mentioned, I am vice president of worldwide regulatory affairs for Merck. In this capacity, I am responsible for interaction with health authorities around the world which oversee the development, the review and approval of Merck's new drug and vaccine products.

Merck has over 4,000 employees living in Montgomery County who are very interested in seeing Merck and the U.S. pharmaceutical industry as a whole continue to be a world leader in the development, discovery and marketing of new medicines and vaccines.

It is important to state from the outset that Merck supports a strong regulatory system, one that assures the safety, efficacy and quality of medicines and vaccines. At the same time, we feel that there are changes in the U.S. regulatory system that are important to allow continued innovation by the U.S. pharmaceutical industry.

We can and should eliminate unnecessary delays and bureaucratic procedures while maintaining high standards for safety, efficacy and quality for new medicines.

We have seven specific recommendations which we would make in the effort to reform regulation. First, FDA should focus on drug approvals. At present, FDA's primary focus is on protecting the U.S. public from unsafe medicines and vaccines. We feel that the agency's resources should also be focused on FDA's positive role in assuring timely availability of new drugs and therapies. Thus, we propose that FDA's mission statement be amended to provide balance between safeguarding the public and promptly approving important new drugs.

Second, we need to eliminate excessive and unnecessary paperwork. The amount of data which is required to be submitted for review by FDA should be limited to what is reasonably required by a competent scientist to make a decision on safety and efficacy. This type of submission has proven to be more than adequate for highly sophisticated European drug regulatory authorities which focus their review on the substantive issues of safety and efficacy rather than auditing or reanalyzing data.

Third, we need to improve FDA management practices. The review process is still too often beset by long review times and delays in approval. We would like to see a managed review process which

sets specific goals and timeframes and a system which holds reviewers and supervisors accountable for meeting timeframes. Such a process would eliminate periods of inactivity, which add nothing to the approval process.

Fourth, as mentioned earlier in your opening comments, Mr. McIntosh, we would like to see an increased use of non-FDA scientists. Currently, FDA employees review an application, write up their findings and make recommendations to supervisors. However, FDA has limited resources for carrying out these activities.

The FDA has already begun experiments with outside reviewing scientists, and these experiments should continue to determine if this review process can lead to more efficient and less costly review without sacrificing quality or continuity. Not only would the participation of academic scientists greatly speed the review process by broadening the pool of experts, but it would also assure that the best scientists reviewed the application.

Fifth, we should eliminate nonessential regulation. Agency procedures should be revamped to eliminate approval requirements for changes in manufacturing processes which add nothing and have no effect on safety or efficacy of products.

We need to realign agency resources along functional lines. Old statutory distinctions between the regulation of drugs and biological products should be eliminated except where there is a clear scientific basis for treating such products differently. At the same time, the parallel and often redundant licensing requirements for biological products should be consolidated into a single application and review process.

Finally, we need to enhance global competitiveness. To optimize the use of our resources, the process of new drug development is most efficiently done on a global basis. In this way, the results of the development program will meet the regulatory requirements of any sophisticated health authority.

Regulatory impediments and inefficiencies to globalizations and manufacturing need to be removed. As an example, companies should be able to base decisions on worldwide sourcing of investigational or marketed drugs based on good business practices, not on the location of a facility.

The American public should expect high standards for safety and efficacy of new medicines and vaccines. Merck has accepted this responsibility and demands from our employees the best science and the best scientific practices.

We do not want to lower the standards for the approval of important medicines and vaccines. Rather, reform should improve management practices and streamline the review process so that we can provide innovative medicines and vaccines to the patients who need them as quickly as possible.

In closing, I would like to thank Congressman Fox for hosting this hearing, and we are pleased that you are taking the lead in examining the issue of FDA regulatory reform, which is so important to maintaining a strong employment base of the research based pharmaceutical industry here in eastern Pennsylvania.

I thank you for being here, and I will answer any questions at the appropriate time.

[The prepared statement of Dr. Blois follows:]

STATEMENT OF DR. DAVID W. BLOIS
MERCK & CO., INC.
SUBCOMMITTEE ON NATIONAL ECONOMIC GROWTH
NATURAL RESOURCES AND REGULATORY AFFAIRS
OF THE
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT
U.S. HOUSE OF REPRESENTATIVES
MONTGOMERY COUNTY COURTHOUSE, ROOM B
NORRISTOWN, PENNSYLVANIA

JUNE 9, 1995

Good morning, Congressman Fox and members of the Committee. My name is Dr. David W. Blois. I am Vice President, Worldwide Regulatory Affairs of Merck Research Laboratories. On behalf of the 4,325 Merck employees who live in your Congressional District, Mr. Fox, I want to express our appreciation for the opportunity to testify here today, and to share our excitement about pharmaceutical innovation. I also want to discuss ways in which the regulatory review process can be changed to facilitate and encourage the rapid introduction of new medicines and vaccines to the American public.

It is important to state at the beginning that Merck supports a strong regulatory system, one that assures the safety, efficacy, and prompt approval of medicines and vaccines. We believe that the Food and Drug Administration (FDA) has an important role to play in this process, and that the Agency has made many important contributions to public health. We have great respect and admiration for the many dedicated scientists in the Agency.

A GROWING DISPARITY EXISTS BETWEEN SCIENCE AND REGULATION

However, there is a growing disparity between a rapidly expanding and increasingly precise science of innovation towards the discovery of new medicines, versus the number of regulations that dampen and restrict pharmaceutical development. The science of drug discovery has led increasingly to more effective and safer medicines, and yet there are regulations and regulatory practices built up over many years which remain in place and which have outlived their usefulness.

Modern medicines are very potent and very specialized compounds, pinpointing specific targets in the body's metabolic pathways and thus attacking—or preventing—diseases with a high degree of efficiency while minimizing side effects. Today's vaccines and medicines are inherently safer than their equivalents of 20 years ago because we have applied our increased knowledge about the fundamental mechanisms of disease and chemistry to their development. Consequently we now can invent highly targeted medicines with very precise mechanisms of action. Modern research focuses on such mechanisms, at a molecular level, that might be involved in the disease

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process. This targeted, rational approach involves experiments with enzymes and cellular receptors to seek potential pharmaceutical compounds, through screening and rational design, that modify the activity of these molecules.

A good example of this evolution is the comparison between ALDOMET, a drug to treat high blood pressure discovered in the 1950's and VASOTEC, a drug discovered in the 1980's to treat the same condition. ALDOMET was discovered by testing compounds directly in animals and patients for lowering blood pressure without knowing the drug's molecular action. VASOTEC was designed using a precise test tube assay that clearly defined its mechanism of action. A patient requires between 1,000 and 2,000 milligrams of ALDOMET for effective treatment whereas a 5 to 10 milligram dose of VASOTEC is highly effective. There is inherently much greater safety for the patient associated with such a low dose of a potent medicine targeted to a precise biochemical mechanism.

However, the regulatory process has not yet been sufficiently modernized to take into account these advances in the discovery process. The review and approval system remains cumbersome and restrictive, almost as if new drug candidates will be less safe and effective than previously was the case. Yet it is clear that the science of the discovery of new prescription medicines has been moving in exactly the opposite direction.

NEW DISEASE TARGETS WILL CHALLENGE OUR INDUSTRY

This is an exciting time for our industry, without question, but a time in which as Merck's own experience illustrates, R&D on complex chronic illnesses is increasingly challenging and costly. The approaches to treatment of the degenerative diseases of an aging population during the next decade will test our skill at molecular engineering and require commitments to R&D of enormous magnitude. In testing drugs in older patients with chronic illnesses, larger trials for longer times are required to insure safety and efficacy. It must always be remembered that innovative pharmaceutical R&D remains synonymous with high risk and high costs.

Looking at just two major disease targets where industry scientists are at work—cancer and AIDS—we can offer an impressive pipeline of hope, but within a constant shadow of potential failure. At Merck, we have research projects to combat these diseases in various stages of development, from early laboratory investigation to full scale clinical investigations.

CANCER: Let me begin with cancer. The field of research for the treatment of cancer is undergoing a dramatic change. Molecular understanding of the metabolic pathways that go awry and cause cancerous growth of cells has progressed dramatically in the last decade.

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Merck's own cancer research is both at an exciting and frustrating stage of drug discovery. In the 1970's, researchers at the National Institutes of Health (NIH) and the National Cancer Institute (NCI) began to track down one of the genes that triggers the runaway growth of human cells that we call cancer. They found that the gene, known as *ras*, plays a critical role in signaling cells to divide uncontrollably and spread cancerous tumors throughout the body.

At Merck, we've produced compounds that block the *ras* signal in test-tube experiments and in just the past months we have made a further advance: we've been able to stop growth of certain tumors in laboratory mice—thus far with none of the toxic side effects of traditional cancer chemotherapy. Our research team continues to search for compounds which are appropriate for testing in humans in blocking the growth of various human tumors.

We are not yet ready to begin clinical trials and there is still a high risk of failure. But a breakthrough could mark a major turning point in the war to help the 7 million victims that cancer strikes annually and save some of the \$104 billion we spend each year in this country to treat it.

AIDS: Merck's AIDS Initiative, ongoing since 1986, is the largest research battle we have ever waged. We have invested hundreds of millions of dollars in discovery research and studied tens of thousands of compounds. Most have failed in the test tube, others have failed in animal studies, and four, to date, have failed in human trials.

In March, however, we announced some very exciting developments about our current sole remaining candidate, the HIV protease inhibitor, CRIVAN, formerly known as MK-639. Our ongoing Phase II trials show that MK-639 has significant antiviral effects and clinical benefits and exhibits a good safety profile. Thus, we have begun Phase III trials with about 3,000 patients.

At the same time, the manufacturing process for MK-639 has proven to be extremely lengthy and complicated. It is the most difficult manufacturing challenge ever faced by Merck. Moreover, the volume requirements are great because the dose is large -- more than 2 pounds per patient per year, which is more than 100 times larger than the dosage of an average Rx medicine. Merck has allocated 125 engineers and more than \$100 million towards the manufacturing changes that will be needed to make this product in sufficient quantities. This is noteworthy because MK-639 has not been approved, and the compound could still fail in Phase III studies.

So much is at stake here. In the U.S. alone, more than 1 million individuals are estimated to be HIV positive; 460,000 have developed AIDS, well over half have died. This tragic toll in human life is mirrored by as much as \$50 to \$70 billion in direct health care expenses and indirect costs to our society every year.

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The unique challenge of AIDS gave birth to a unique partnership among 17 pharmaceutical companies. In April 1993, these companies—led by Merck—formed the Inter-Company Collaboration for AIDS Drug Development. Our goal is to accelerate the development of new drugs and identify therapeutic combinations that will significantly advance the treatment of HIV infection. Such studies are actually underway.

INCREASED MARKET COMPETITION INCREASES THE RESEARCH STAKES

Clearly, to maintain our historic level of innovation, we must meet and master the challenges confronting our industry today. These challenges include both unlocking the mysteries of disease through science and adapting our discovery and business objectives to an increasingly competitive marketplace.

It is no secret that the economics of health care have changed substantially over the past decade. For example, just eight years ago, managed care customers, including HMO's and the government, accounted for about 30 percent of Merck's sales; today about 70 percent of our drugs go to that market. There has also been a consolidation in the number of drug and biotechnology companies with scientists at work in laboratories in America. In short, the new market environment places an even greater premium on every promising lead.

FDA REFORM IS CRITICAL FOR INNOVATION

This is why FDA regulatory reform plays such a critical role in continued innovation by U.S. industry. Streamlining the regulatory procedures and FDA management practices to achieve even small improvements in the drug development and approval process can pay off in enormous human and economic dividends. We can and should eliminate unnecessary delays and bureaucratic procedures while maintaining high standards for safety and efficacy of new medicines and vaccines. Let me give you some illustrations of the type of changes that could be made.

1. Refocus the Agency on drug approval

Redirecting the Agency's resources should begin with a statutory revision of its mission statement to stress FDA's positive role in assuring the timely availability of new drugs and therapies. As part of a revised mission statement, recognition and support should be given to those at the FDA who play an important role in approving important new medicines and vaccines.

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2. Eliminate unnecessary paperwork

The amount of data required for submission and subsequent review by the FDA should be limited to what is reasonably required to determine safety and efficacy. The Agency should accept comprehensive summary data (which could be subsequently audited), rather than require 100 percent of the raw data resulting from clinical trials. This process has proven sufficient in other highly effective European drug regulatory systems and has greatly speeded reviews and has focused those reviewed on the substantive issues of safety and efficacy rather than on auditing or re-analyzing an applicant's data.

3. Improve Management Practices

The review process is still too often beset by long review times and delays in approval. There is a diffusion of responsibilities, long down times when little action is occurring and a lack of delegation of authority. We would like to see a managed review process which sets specific goals and milestones and a system which holds reviewers and supervisors accountable for meeting the timetables. Such a process would prevent long periods of inactivity and the attendant delays in approvals.

4. Contract out selected review functions

It is clear that FDA resources are limited for the amount of work its scientists must do. Currently, FDA employees review all parts of a new drug application, or a supplemental new drug application, write up their findings and make recommendations to their supervisors. While agency reviewers are knowledgeable and efficient, a much larger and broader group of reviewers is available in the academic, scientific and medical communities.

Experiments with outside reviewers have begun and should be continued to determine if the review process can be expedited, made more effective, and less costly without loss of quality or continuity. The scientific information contained in a new drug application or a supplemental NDA could be processed by an FDA supervisor and then sent to academic scientists in the best medical centers around the country for evaluation. I believe that academic scientists would relish such a role in new drug discovery. Not only would their participation greatly speed the review process by broadening the pool of experts, but it would assure that the best expertise nationally was applied to each application. The process, if managed properly, could enhance judgments of the safety and efficacy of new medicines and vaccines.

This process is an extension of what is actually done today in that FDA utilizes outside Advisory Committees for evaluating safety and efficacy. Advisory Committees comprised of outside experts, and other outside contractors, such as the MITRE Corporation, have proven that outside reviews are possible and can work well. Extending the concept further makes good sense and initiative should be made to try

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such extensions as an evolution of the process. Deadlines could be given to outsider reviewers to insure timeliness and their remuneration for reviews linked to the timeliness of the review. If outside reviews work without loss of quality or continuity, this proposal would potentially greatly reduce FDA costs by shifting a greater responsibility to the private sector.

5. Eliminate non-essential regulation

Agency procedures should be revamped to significantly revise the regulations requiring the submission and approval of even minor changes in manufacturing procedures for drugs and biologicals. These revisions can be made without any impact on the safety and efficacy of the product. Here also, the FDA should allow for external review of supplemental applications containing clinical data. Since the product is already on the market and has been proven safe, this cost-effective approach would free FDA resources for critical functions that cannot be delegated.

6. Realign Agency resources along functional lines

The approval process for drugs and therapeutic biologicals, i.e., those with the same therapeutic use as manufactured drugs, should be combined. Old statutory distinctions between the regulation of drugs and biological products should be eliminated, except where there is a clear scientific basis for treating such products differently. At the same time, the parallel and often redundant Establishment License Application (ELA) and Product License Applications (PLA) for biologics should be consolidated into a single review process.

7. Enhance Global Competitiveness

In light of the significant resources required for the development of a new drug, this development is most efficiently done on a global basis so that the program will meet the regulatory requirements of any sophisticated regulatory authority. The FDA is actively involved in the tripartite International Conference on Harmonization (ICH) process to standardize the regulatory requirements among Japan, Europe and the United States. This effort needs to continue.

Regulatory impediments and inefficiencies to globalization of research and manufacturing need to be removed. We should make decisions on worldwide sourcing of investigational drugs used in clinical trials and for locating our manufacturing facilities based on good business decisions, not on the geographic location of a facility. The Congress should revise the Drug Export Amendments Act of 1986 to allow U.S. companies to export any product (including veterinary medicines) to a country in which the product has received the appropriate regulatory approval. In addition, memoranda of understanding should be established with overseas regulatory authorities that would

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allow for mutual recognition of the inspections of clinical investigators and manufacturing. This would help free FDA employees from conducting costly and time consuming inspections overseas.

CONCLUSION

The American public should expect standards for safety and efficacy for new medicines and vaccines that are the most stringent of any nation's. Merck has always accepted this responsibility and demands from our employees the best science and the best scientific practices. We do not want reform to lower standards for the approval of important medicines and vaccines. Rather, reform should improve management practices and streamline the review process so that we can provide innovative medicines and vaccines to the patients who need them as quickly as possible.

Today, I have presented some examples of change that the Congress needs to ensure are made to the FDA. We are working with our research colleagues from companies in the Pharmaceutical Research and Manufacturers of America (PhRMA) to develop more comprehensive and specific recommendations. We are also eager to consider the ideas and work with others in the public and private sectors who are currently developing reform proposals.

Again, I thank you for the opportunity to be here today and look forward to your questions.

Mr. McINTOSH. Thank you very much, Dr. Blois. I apologize for mangling your name earlier.

Our second witness is Dr. James Molt, who is here today with Rhone-Poulenc Rorer.

Dr. Molt.

Mr. MOLT. My name is James Molt. I am the head of regulatory affairs for Rhone-Poulenc Rorer or RPR. We are a research intensive U.S. company located here in the 13th Congressional District in Collegeville, PA.

Because RPR's mission is the discovery and development of new medicines, we have frequent interactions with the Food and Drug Administration. We appreciate this opportunity to offer some ideas that may help improve the drug approval process.

As you know, pharmaceutical research is a risky, costly and lengthy process not only for us as companies, but also for the patients who are waiting for these important new medicines. Today I would like to use as examples two new medicines that we are developing to see where we may be able to improve FDA, but also to show where we think FDA has some strengths.

The goal, of course, is to get new medicines to the patient faster. Let me start with the example of Rilutek, where we have had some positive interactions resulting from some recent FDA self-initiatives for reform.

As we heard early in the very poignant remarks from Mariah Gladis, Rilutek is the first compound shown to prolong survival in ALS. Since there is no approved treatment for ALS, RPR has asked FDA to allow patient access before the drug is approved through a treatment IND. The treatment IND is a mechanism put in place by FDA to allow a patient access to promising new drugs before the final approval is granted. We believe that this is a positive step toward getting drugs to patients faster.

We hope that because the drug is available under a treatment IND there remains an incentive for FDA to provide full approval. It is this concept of incentives that really brings me to my main point today.

Until this system of incentives at FDA is modified, patients will not have full access to all the medicines that could be available to them. It is this concept of patient value—that is, the benefit to be gained versus the risk associated with using the medicine—that I would like to focus on.

As you are well aware, a drug is approved by FDA if they determine that the weight of the benefit outweighs the weight of the risk. For a number of reasons, FDA has historically focused on the risk side of the balance so that very little risk is able to pull down a drug, even though there may be substantial balance.

One of the previous questions was whether Thalidomide had anything to do with this, and I think the question is yes, it did. That is one of the reasons that FDA does focus very intently on risk. We see a little bit of risk being able to pull down a lot of benefit. We really cannot fault FDA for this because I think it is we, the public, who have placed on FDA an incentive system that really rewards caution.

Let me give you an example using our new anticancer agent, Taxotere. Taxotere has been shown to provide significant benefit in

women with advanced breast cancer. It has been shown to work even after other chemotherapy has failed. I think the absence today of Beverly Zakarian shows that breast cancer is a particularly devastating disease where new therapies are sorely needed.

We submitted an NDA for Taxotere to FDA last July. FDA reviewed the application in a very commendably fast 4 months. FDA arrived at the conclusion that the benefit of Taxotere did outweigh its risk.

The drug approval system in the United States is cautious. FDA usually does not act alone. For major decisions, they seek a second opinion from an independent board of experts known as an advisory committee.

For Taxotere, the advisory committee pointed out to FDA the risk side of the equation without doing too much to reinforce the benefit. In the end, the advisory committee offered equivocal advice on whether or not to make the drug available.

Without a strong vote of support from their advisory committee, FDA did not act on their previous conviction, and Taxotere remains unapproved today while FDA continues to ask for more information about the risks of the compound.

It is clear that the system, and that includes FDA and its advisory committees, and it is a system which is cautious, will produce fewer new drugs than one that has its goal to make more drugs available to the patient. This caution stems partly from fear of public retribution for approving a drug that turns out to have a side effect profile that was different or greater than what FDA thought it was.

To change FDA, we must change their incentive system. FDA has to have less fear of public retribution for underestimating the true risk of a drug and be more sensitive to the needs of the patients who need therapies.

Mr. MCINTOSH. If I could ask you to go ahead and summarize?

Mr. MOLT. I am.

Mr. MCINTOSH. Thank you.

Mr. MOLT. This is the hard part. How are we going to make this happen? Certainly one answer is to rewrite the laws under which FDA operates. Another, and it is not necessarily exclusive, is to increase congressional oversight and perhaps consolidate jurisdiction over FDA into one committee. Congress should focus on creating an environment where inaction by FDA is as much a cause for investigation as a bad action.

We know the change in FDA will not be easy, but we are encouraged by the efforts such as those made by Congressman Fox and you. We at RPR are ready to help in any way possible.

We realize that there is a real opportunity to make lasting, constructive changes to FDA that will be of benefit to the patients. It is very clear from what we need today that the patients are waiting.

[The prepared statement of Mr. Molt follows:]

TESTIMONY OF JAMES T. MOLT, Ph. D
U.S. HOUSE GOVERNMENT REFORM & OVERSIGHT COMMITTEE
June 9, 1995

Good Morning. My name is James Molt. I am the head of Worldwide Regulatory Affairs for Rhône-Poulenc Rorer. Rhône-Poulenc Rorer is a U.S. corporation, headquartered in Collegeville, Pennsylvania, dedicated to the discovery, development, manufacturing, and marketing of human pharmaceuticals. I hope you will not mind, but to save everyone's time, I will refer to my company by using the initials "RPR" instead of Rhône-Poulenc Rorer, for the balance of my brief remarks. In 1994 RPR invested \$600 million, or 15% of sales on research and development. RPR's research programs are focused on six therapeutic areas: Cardiovascular Diseases, Central Nervous System Disorders, Infectious Diseases, Cancer, Respiratory Diseases, and Bone Metabolism/Rheumatology. Because of RPR's dedication to the discovery of medicines that will improve human health and the quality of life of people throughout the world, and because of my often rewarding but sometimes frustrating experiences in dealing with drug regulatory agencies, I really appreciate this opportunity to talk about what can be done to re-engineer and streamline the drug approval process in the United States. For that reason, I want to thank Congressman Fox for providing this forum, and members of the Committee and staff for having me here today.

Pharmaceutical research is an extremely risky, costly, and lengthy process, not only for my company, but also for the patients that are waiting for the development and approval of important new medicines. Rilutek and Taxotere® are the brand names of two potentially important new therapies in our near-term research pipeline. We are very hopeful that we will receive

approvals of our New Drug Applications (NDAs) for Rilutek and Taxotere® from the U.S. Food and Drug Administration (FDA) later this year. I will use these two products to illustrate areas where we see strengths in the FDA process and conversely where we see opportunities for significant change with the goal being a better and more responsive FDA.

Let me start with the example of Rilutek where we have seen some positive results stemming from recent FDA initiatives for self-reform. Rilutek is indicated for the treatment of amyotrophic lateral sclerosis or ALS, which is also known as Lou Gehrig's Disease. Generally patients survive three to five years after diagnosis. There are approximately 30,000 ALS patients in the U.S. Results of the largest ever Phase III trial conducted in ALS, demonstrated that Rilutek is the first compound to prolong survival in this disease. Since there is no approved treatment for ALS, RPR has submitted documentation to FDA to allow patient access to Rilutek under a Treatment IND, before full marketing approval is potentially granted. The Treatment IND is a mechanism put in place by FDA to bring promising new drugs to the public before the NDA is approved. We concur with the statements made by William Shultz, Deputy FDA Commissioner for Policy, in his recent testimony before Congress that initiatives such as Treatment INDs help FDA accomplish its "twin goals of protecting the public and promoting the rapid availability of effective drugs". Our one concern is that patient access through a Treatment IND does not become a disincentive for FDA to approve the NDA. It is this concept of incentives for FDA that brings me to my main point.

Until the system of incentives at FDA is modified, patients in need in the United States will not have full access to all the medicines that could be of the net beneficial value to them.

Its this concept of net beneficial value, what we refer to as the benefit/risk assessment, and what Deputy Commissioner Shultz called "promoting the rapid availability of effective drugs" versus "protecting the public", that I would like to focus on. It is our perception that for FDA the benefit/risk assessment has historically focused on risk. We cannot fault FDA for this because we, the public, have placed on FDA an incentive system that rewards it for being cautious but does little to provide incentives to increase the availability of beneficial medicines. Until the incentive system changes, we should not expect FDA to act any differently than they do now.

Let me give you an example of our experience with FDA with regard to this benefit/risk assessment. For this example I will use our anti-cancer agent Taxotere®. Taxotere® has been shown to provide significant benefit in women with advanced breast cancer where other chemotherapies have failed. And breast cancer is a disease where new therapies are sorely needed. Each year in the U.S., more than 180,000 women are diagnosed as having breast cancer, and this year 46,000 will die from the disease.

We submitted a New Drug Application for Taxotere® in July of last year based on a developmental program devised in conjunction with FDA. FDA reviewed the application in about 4 months, which is very fast and, again, commendable. At the end of that review the Agency had arrived at the conclusion that the considerable benefits of this drug for women with resistant breast cancer outweighed its risks. This was a difficult decision because, as with all highly active anticancer agents, the side effects are substantial. As is usually the case the FDA decided to use an Advisory Committee to obtain an independent opinion on the approvability of the compound.

And that is where we come to another problem. Because historically the FDA is castigated in public if they underestimate the risk of a drug, they seek to indemnify their decisions by using an Advisory Committee. In the case of Taxotere®, the Advisory Committee was quick to point out the toxicity profile of the compound without acknowledging the benefit; and the Committee ultimately provided FDA with equivocal advice on whether or not to make the drug available for women with advanced resistant breast cancer. Without a strong vote of support, FDA was not able to act on their previous conviction and Taxotere® remains unapproved today while FDA continues to analyze the data we submitted to them. And, except for the strong voices coming from the sufferers of breast cancer and their supporters, no one is asking FDA how much potential benefit is being withheld from the patients by their inaction.

It is clear that FDA and its Advisory Committees, because they both appear to focus on risk at the expense of benefit, are in need of reform. We must envision a system where there is a reward for approval of drugs that are able to save the lives of Americans. FDA has to have less fear of public retribution for a bad decision. Not making a decision, as in the case of Taxotere®, can be more detrimental to the public health than the extremely rare bad decision. Likewise, if the present Advisory Committee system is to remain intact, it too must place proper balance on the benefit to risk analysis of high potency, life saving drugs. We must work to foster a system of drug approval that will bring maximum benefit to patients while assuring that the risk of use is acceptable. Until now the risk side of the equation has been of paramount importance. Any FDA reform must include proper incentives not to hold up approval of drugs deemed to provide clinical benefit when FDA has decided that the benefits outweigh the risks.

Now the hard part. How do we bring this about? Certainly one answer is to rewrite the laws under which FDA operates. Another answer is to increase Congressional oversight, and perhaps to consolidate the jurisdiction of those Congressional Committees that have control over FDA into one Committee. Congress should focus on creating an environment where inaction by FDA is as much a cause for an investigation as is a bad action. And while we need to move, we need to do it in a way that will provide lasting change. To use re-engineering terms, a few "quick hits" are probably valuable, but meaningful change must take place at a pace where it can be assimilated. We know that reforming FDA will not be easy, but we are encouraged by efforts such as those made by Congressman Fox here today. We at RPR thank you for this opportunity to share our concerns and views regarding FDA reform with you today and are ready to help in anyway.

Mr. MCINTOSH. Thank you very much, Dr. Molt.

Our next witness on this panel is Dr. Robert Powell, who is the vice president and director of regulatory affairs for SmithKline Beecham Pharmaceuticals.

Dr. Powell.

Mr. POWELL. Thank you, Mr. Chairman. Mr. Chairman and Mr. Fox, I would like to thank you for the opportunity to testify before this committee.

SmithKline Beecham is one of the world's largest healthcare companies. We discover, develop, manufacture and market human pharmaceuticals, including innovative childhood and adult vaccines, over the counter medicines, health related consumer products and clinical laboratory testing services.

We are a very large employer in the Commonwealth of Pennsylvania with over 6,500 employees, including over 1,700 employees in the 13th Congressional District.

When I joined the pharmaceutical industry well over 30 years ago, things were considerably less complicated than they are today. This is true not only from the point of view of the complexity of drug development, but from the complexity of drug regulations as well.

The combination of these two evolving and increasing complexities has made the development of useful new drugs an extremely formidable task and has added considerable expense and time in getting useful new therapies to the American public. In fact, it now takes on average well over 10 years to conduct the studies necessary to support a new drug application.

During this time, the FDA is directly involved with every aspect of the development. Nevertheless, in 1994, it took an average of 19 months for the agency to evaluate new drug applications that were submitted at the end of the development process.

This is not to say that FDA has been unresponsive to the growing problems of complexity in the development of drugs. As a matter of fact, as a result of the implementation of user fees and the specific performance goals associated with them, the current 19-month average review time represents a reduction of review time from the approximately 30 to 33 months that was standard for the 12 years prior to 1994.

Nevertheless, other sophisticated regulatory agencies are able to review the safety and efficacy of new drugs considerably more rapidly. For example, the United Kingdom approves new drugs following an average of 6 months of review, 1 year faster on average than FDA, and these applications are generally based on the same data base as those in the United States.

It is the consumer, of course, who must ultimately bear both the economic and social cost of delays in the availability of useful new therapies resulting from the system that has evolved over the 33 years since the 1962 drug amendments.

There is perhaps an even greater price to be paid for the increasing complexity and cost of drug development. Some drugs may never be developed at all.

In the next few minutes, I would like to suggest some ideas that I believe would improve the drug development process in the United States without compromising patient safety. Let me assure you

on this latter point. We in the drug industry are fully aware of the important role played by FDA in protecting consumers in matters of public health and would in no way wish to see the FDA disbanded or rendered impotent in carrying out this portion of its mission.

It is of interest that although the FDA traces its roots back to the 1830's, it has never had a congressionally approved mission statement. Thus, my first recommendation for FDA reform consists of a legislative mandate that clearly describes the mission of FDA in terms of what it should do and the balance it should have between enforcement and insuring the availability of important new drugs.

I would propose that the following key elements be part of that mission statement: To facilitate a timely availability of safe and effective drug products; to encourage efficient drug development; to take prompt action to avoid inappropriate health risks; to assure global harmonization of safety and efficacy standards; and to facilitate the flow of medical information.

However, the mere statement of a mission is not sufficient. Senior managers of FDA come and go, and with them the enthusiasm for one or another of individual mission statements may wax or wane. Thus, as a second initiative and equally important to the first, I would recommend the creation of a policy and performance review commission to oversee the operation of FDA.

This commission would consist of persons not employed by the Government, but expert in drug development and drug use in the United States. This proposed commission would have the power to recommend policy and personnel changes within the agency as the result of an observed failure to perform consistently in concert with the letter and spirit of the mission statement.

While such a commission would report directly to the Secretary of HHS, an annual report to Congress of its findings and recommendations would assure appropriate congressional oversight that the commission is effectively providing the necessary focus of the FDA on the availability of safe and effective new therapies to American consumers.

There are, of course, several other initiatives that might provide incremental improvement to the function of the FDA, and I would support those mentioned by previous speakers.

Due to time constraints today, I would suggest that if only three initiatives were implemented—the mission statement, the policy and performance review committee and the elimination of detailed data verification as suggested by Dr. Blois—the entire process would be vastly improved to the great benefit of and with no additional risk to the American public.

Thank you for your kind attention.

[The prepared statement of Mr. Powell follows:]

STATEMENT OF

ROBERT L. POWELL, Ph.D.

**Vice President, Regulatory Affairs, North America
SmithKline Beecham Pharmaceuticals**

to Special Field Hearing

House Government Reform and Oversight Committee

June 9, 1995

Norristown, PA

My name is Robert Powell, Vice President and Director, Regulatory Affairs, for SmithKline Beecham Pharmaceuticals. On behalf of SB, I would like to thank you, Representative Fox, for letting us take part in this hearing on FDA reform.

SmithKline Beecham is one of the world's largest health care companies; SB discovers, develops, manufactures and markets human pharmaceuticals, including innovative childhood and adult vaccines, over-the-counter medicines, health-related consumer products and clinical laboratory testing services. We are a very large employer in the Commonwealth of Pennsylvania, with over 6500 jobs. Our U.S. headquarters, and the U.S. headquarters of all of our major businesses are located in Pennsylvania, including over 1700 jobs in the 13th Congressional District.

I joined the Pharmaceutical industry almost 30 years ago, a time when things were considerably less complicated than they are now. This is true not only from the point of view of the "science" of drug development, but also from the point of view of the complexity of the regulation of that drug development. The combination of these two gradually changing environmental complexities has made the development

of useful new drugs an extremely formidable task, and has added considerable expense and time in getting useful new therapies to the American public.

In fact, it now takes, on average, well over 10 years from the time a drug is "discovered" until it becomes available for general use by patients. During this time, the agency is directly involved with every aspect of the development. Nevertheless, it took 19 months for the agency to evaluate the average New Drug Application in 1994. This is not to say that the FDA has been totally unresponsive to the growing problems of complexity in the development of drugs. As a result of the implementation of user fees and the specific performance goals associated with them, this 19 month review average represents a reduction of review time from the approximately 30 to 33 months that was standard review time for the 12 years prior to 1994.

Nevertheless, other sophisticated regulatory agencies are able to review the safety and efficacy of new drugs considerably more rapidly. (For example, the United Kingdom approves new drugs based on essentially the same data base as the U.S., following an average of 6 months of review. This difference alone accounts for over a 12 month "drug-lag," on average.) It is the consumer, of course, who ultimately must bear not only the economic cost of drug development but also the social cost of delays in the availability of useful new therapies because of the system that has evolved over the past 33 years since the 1962 Drug amendments.

But there is, perhaps, an even greater price to be paid for this increasing complexity and cost of drug development. Some drugs may never be developed at all because of the inability to obtain capital to support such an expensive process, the return on

which is at least in part dependent on obtaining approval for marketing of the resulting drug product from an ever more complicated, overworked and understaffed bureaucracy which is the current Food and Drug Administration.

It is this aspect of the problem that I would like to address briefly today. In the next few minutes, I would like to suggest some ideas that would improve the drug development process in the United States without compromising the risk to consumers. Let me assure you on this latter point. We, in the drug industry, are fully aware of the important role played by FDA in protecting consumers in matters of public health, and would in no way wish to see the FDA disbanded or rendered impotent in carrying out this portion of its mission. But, there are other aspects of the role of FDA in today's society which also need to be stressed.

Although the FDA traces its roots back to the 1830's, it has never had a Congressionally approved mission statement.

Thus, my first recommendation for FDA reform consists of a legislative mandate that clearly describes the mission of FDA in terms of what it should do, and the appropriate balance it should have between enforcement and assurance of the availability of important new drugs. We would propose that the following be the key elements of that "Mission Statement":

- 1) To facilitate the timely availability of safe and effective drug products;
- 2) To encourage efficient drug development;
- 3) To take prompt action to avoid inappropriate health risks;
- 4) To assure global harmonization of safety and efficacy standards; and
- 5) To facilitate the flow of medical information.

However, the mere statement of a mission is not sufficient, since managers of FDA come and go and with them enthusiasm for one or another of the individual mission statements may wax or wane. Thus as a second initiative, equally important, would be creation of a "Policy and Performance Review Commission" to oversee the operation of the FDA. This commission would consist of persons not employed by the government, but expert in drug development and drug use in the United States. The commission would be responsible for review of policies created by FDA and for the performance of the agency in the context of assuring the implementation of its stated mission. The commission would have the power to recommend policy changes within the agency as a result of an observed failure to perform consistently in concert with the letter and the spirit of the mission statement. While such a commission would report directly to the Secretary of HHS, an annual report to Congress of its findings and recommendations would enlist appropriate Congressional oversight for further assurance that the commission is effectively providing the necessary focus of the FDA on the availability of safe and effective new therapies to American consumers.

A third proposal that I would like to make is that the agency should look into utilization of outside experts to help speed up the review process. Use of qualified external resources would help overcome FDA's difficulty in attracting and retaining

scientific and medical personnel due to the highly competitive nature of the demand for these same resources by the drug industry, as well as colleges and universities. Scientists, who for a number of reasons are drawn into academia, private practice or other private (non-drug industry) endeavors, should be made available on a contractual basis to review data and information on the safety and efficacy of new therapies. They could provide advice to the agency on making the appropriate decisions on the availability of these medications to practicing physicians in the United States.

A final suggestion is that the agency reengineer its process for drug safety and efficacy review. Currently, FDA requires submission of not only detailed analyses and summaries of the data and information collected during the development of drug products, but also all of the supporting data and documentation related to those summaries and analyses. This requirement results in an application which literally consists of a "truckload" of paper, or its equivalent in electronic media, which, in turn, must be reviewed by the FDA staff. (For example, it is not unusual for an application to consist of over 900 volumes of material, whereas the same application submitted to the British authorities would typically consisted of fewer than 50 volumes.

We would propose a system of certification of the analyses and summaries (based on the raw data retained by the sponsor and subject to inspection by the agency in the event of the need for verification) and the elimination of full data submission and verification by the FDA review staff. We believe that this is a redundant and unnecessary task which consumes considerable time and resources, and provides no further assurance of the credibility of the database on which the analyses are based.

A switching to such certified summary submission -- as is the practice in many other sophisticated countries -- would add great efficiency to the FDA review process, whether done "in house" or by an outside consultant under contract to the agency.

There are, of course, several other initiatives that would provide incremental improvement in the function of the FDA, which are being thoroughly discussed and considered by us and others in healthcare. We at SmithKline Beecham are participating in these discussions, and will comment on other proposals in due course. But for today, I would suggest that if only these four initiatives were implemented (The Mission Statement; The Policy and Performance Review Commission, Use of Outside Experts in the Review Process, and Elimination of Detailed Data Verification by the Reviewer), the entire process would be vastly improved to the great benefit of, and with no additional risk to, the American public.

Thank you for your kind attention. If there are any questions, I would be happy to attempt to answer them.

Mr. McINTOSH. Thank you very much, Dr. Powell. I appreciate your testimony today.

Our next witness on this panel is Mr. Bruce Carroll, who is the manager of government relations for Centocor.

Mr. Carroll, thank you for joining us.

Mr. CARROLL. Thank you, Chairman McIntosh and members of the committee.

My name is Bruce Carroll, manager of government relations at Centocor, the largest biotechnology company in Pennsylvania located in nearby Chester County. Our president and chief executive officer, David Holveck, was unable to be here today, so I am presenting testimony on his behalf.

Centocor employs over 300 people in our Chester County facility and nearly 600 total worldwide. We focus on the development, manufacturing and marketing of diagnostic and therapeutic products, and they include products for cancer, cardiovascular disease and infectious disease.

It is fair to say that Centocor has had an overall positive experience with the FDA. For example, approval of our first therapeutic, a cardiovascular drug called ReoPro, was accomplished in an extraordinarily speedy matter with final approval coming just 1 year after initial application.

Today, however, I would like to talk about the device side of our company and the FDA. Centocor also produces in vitro diagnostic tests, which are the routine laboratory tests that everyone goes through that is part of a physical exam. Centocor's tests are used in the management of ovarian, pancreatic, breast, lung and other types of cancers.

After investing 10 years and \$20 million seeking FDA approval for these products, only one Centocor product, and that is an ovarian cancer test, has ever been approved for use in the United States. That is because these blood tests are regulated by the FDA in a category of medical device known as class III, which is designed for high risk devices such as heart valves, pacemakers, certain devices implanted into the body and devices which are used for life sustaining or lifesaving purposes.

These products are also subject to the highest levels of regulatory control. Unlike other class III products which are critical to maintaining human health, our blood tests do not have the potential to be intrinsically unsafe because they are never used in the body and are not used as the sole basis for medical decisionmaking.

FDA approval of a class III IVD test requires submission of data from extensive evaluations, which for products like ours take many years to complete and which ultimately cost many times the annual expected revenues for the product.

As a partial remedy, Centocor recently filed a petition with the agency seeking reclassification of a limited number of IVD tests. The agency has been supportive of that initially. We would welcome any assistance from this committee to further that initiative with the agency.

A more complete solution to the issue of unnecessarily strict regulation of these blood tests can be accomplished through legislation. Again, we ask Congress to consider reclassifying these types of IVD's from class III to class II, while at the same time giving

FDA the discretion to put specific products in class III if they feel it is needed.

One final note of interest regarding regulation of IVD's. We have studied the citizens petition recently filed by the Indiana Medical Device Manufacturers Council regarding the FDA's development of guidance and other similar documents. We would like to add our support to the observation that guidance can play a most useful and valuable role when the FDA takes the time to involve the public in the initiation, development and implementation of those documents.

Well developed guidance helps reduce industry's cost and time requirements when preparing premarket submissions. For guidance documents to play that role, however, the public needs to contribute to the process by which they are created so that the FDA decisions are well informed.

Obviously, IVD over regulation is a specific problem that the diagnostic component of the medical technology industry faces. We also support efforts from HIMA, the Health Industry Manufacturers Association, and BIO, the Biotechnology Industry Organization, and their efforts for FDA reform proposals.

Three other items that we are interested in which HIMA and BIO are supporting are restructuring the overlapping procedures between CBER and CDER within the FDA; reforming the FDA regulations on exporting, and that includes support of H.R. 1300 introduced by Congressman Upton; and reform of the FDA marketing procedures.

One quick example is our new heart drug. The launch of the drug was held up because the size of the generic brand was not exactly 50 percent of the final size of the brand name itself. That is why we are interested in the marketing procedures aspect of the FDA.

In closing, on behalf of Mr. Holveck and the employees at Centocor, I want to thank the members for focusing on this crucial public policy issue. Mr. Holveck has stated numerous times that he believes a sensible, market friendly, incremental approach to FDA reform is the best way to move forward.

We in the medical technology industry will continue to drive ahead to innovate and create products that meet unmet medical needs such as cancer, arthritis and heart disease. We need a well run and market driven regulatory process to help make that happen.

Thank you.

[The prepared statement of Mr. Carroll follows:]

Testimony of Bruce Carroll
Manager of Government Relations
Centocor, Inc.
Before the United States
House Committee on Government Reform and Oversight
Subcommittee on National Economic Growth, Natural Resources,
and Regulatory Affairs
June 9, 1995

Thank you Mr. Chairman for the opportunity to testify today. Good morning members of the subcommittee. My name is Bruce Carroll, Manager of Government Relations at Centocor, the largest biotechnology company in Pennsylvania, located in nearby Chester County. Our President and Chief Executive Officer, David Holveck, was unable to be here today, so I am presenting testimony on his behalf.

I am pleased to discuss some of the issues facing the health care technology industry and to suggest a few reasonable and achievable ways to improve the role that the Food and Drug Administration plays in making new and innovative technologies available in the U.S. and abroad.

Centocor employs over 300 people in our Chester County facility and nearly 600 total worldwide. We focus on development, manufacturing and marketing diagnostic and therapeutic products for human health care which are used in managing patients with infectious, cardiovascular and autoimmune diseases, and cancer.

It is fair to say that Centocor has had an overall positive experience with the FDA. For example, approval for our first therapeutic, a cardiovascular drug called ReoPro, was accomplished in

an extraordinarily speedy manner with final approval coming just one year after initial application.

In addition to therapeutic products, Centocor is the world's leading producer of *in vitro* diagnostic tests -- or IVDs -- used in the management of cancer patients. IVDs are the routine blood and urine tests which all of you have experienced as part of a physical examination. It is in the area of regulating IVDs that we feel substantial changes should take place at the FDA. Because, after investing nearly 10 years and 20 million dollars seeking FDA approval for these products, only one Centocor product has ever been approved for use in the United States. Accordingly, the vast majority of our commercial activity and a significant portion of our high-skill manufacturing base is located abroad where these products have been used successfully for many years.

Centocor's tests are used in the management of ovarian, pancreatic, breast, lung, and other types of cancers. FDA regulates cancer diagnostics under its premarket approval (PMA) authority -- the most stringent regulatory control. Medical device and diagnostic products, like Centocor's blood tests, are the building blocks in the search for therapeutic products. As these diagnostic tools are researched and developed, clues surface in the ultimate hunt -- the cures for cancer, AIDS and other killer diseases. That is why it is critical that regulatory reform focuses on this area of medical technology. What we are developing today in the area of blood tests has a direct impact on providing health therapies in the coming years.

However, these blood tests are regulated by the FDA in a category of medical device known as "Class III" -- which is designed for high-risk devices such as heart valves, pacemakers, certain devices implanted into the body and devices which are used for life-sustaining or life-saving purposes. These products are also subject to the highest levels of regulatory control. Unlike other

Class III products, which are critical to maintaining human health, our blood tests don't have the potential to be intrinsically unsafe because they are never used in the body and are not used as the sole basis for medical decision making. FDA approval of a Class III IVD requires submission of data from extensive evaluations which, for products like ours, take many years to complete and which often cost many times the annual expected revenues for the product.

As a partial remedy, Centocor recently filed a petition with the agency seeking reclassification of a limited category of IVD products. And the agency has been very supportive of this initiative. Unfortunately, the administrative procedures necessary to accomplish the reclassification have historically taken many years to complete. We would welcome any assistance this committee can provide in improving the speed by which this process moves.

A more complete solution to the issue of unnecessarily strict regulation of new IVDs can be accomplished through legislation. We encourage this subcommittee to consider legislation which automatically places all new IVDs into Class II, while at the same time retaining FDA's discretion to place new IVDs which raise significant new issues of safety and effectiveness, in Class III.

One final note of interest regarding regulation of IVDs. We have studied the Citizens Petition recently filed by the Indiana Medical Device Manufacturers Council regarding the FDA's development of guidance and other similar documents. We would like to add our support to the observation that guidance can play a most useful and valuable role when the FDA take the time to involve the public in the initiation, development and implementation of those documents. Well-developed guidance helps reduce industry's cost and time requirements when preparing premarket submissions. They also speed the review and clearance by FDA reviewers of those submissions

because they establish clear criteria for decision-making during scientific review. For guidance documents to play that role, however, they public needs to contribute to the process by which they are created so that the FDA decisions are well-informed.

Obviously, IVD over-regulation is a specific problem that the diagnostic component of the medical technology industry faces. We also fully support HIMA and the Biotechnology Industry Organization (BIO) in their efforts to move forward on FDA reform proposals. Some areas which we feel are most important include:

- Restructuring the overlapping procedures between the Center for Biologic Evaluation and Review and the Center for Drug Evaluation and Review (CBER and CDER). There are many confusing and contradictory regulations which biologic companies must maneuver through on the way to product application and approval. Those regulatory hoops are putting biologic companies at a competitive disadvantage. We fully endorse the proposal by BIO to merge biologic regulations under the Public Health and Service Act into the Food, Drug and Cosmetic Act. This proposal also addresses the differing manufacturing standards between drugs and biologic therapies.

- Reforming the FDA regulations on exporting. Current FDA exporting regulations are driving manufacturing jobs and life-saving medical products overseas. Changing these regulations is essential for keeping American medical technology in this nation, and not forcing companies to move operations overseas. Centocor supports HR 1300, introduced by Congressman Fred Upton, which would eliminate the FDA-approval of exporting products going to GATT Treaty nations. I would also like to thank Chairman McIntosh for his support of this legislation as well.

- Reform of FDA marketing procedures. The agency's restrictions on marketing and promotion have gone beyond the bounds of their original intent. Centocor, in its move toward launch of ReoPro this year, found this out first hand. We believe that the industry's marketing practices must comply with FDA standards, but the current process is slow and bureaucratic. Again, we endorse BIO's proposal to curtail items such as exempting press releases involving SEC requirements, and prohibiting prior FDA approval of advertising or sales literature for the first 120 days of a launch.

In closing, on behalf of Mr. Holveck and all of the employees at Centocor, I want to thank the members for focusing on this crucial public policy issues. Mr. Holveck has stated numerous times that he believes a sensible, market-friendly, incremental approach to FDA reform is the best way to move forward. Wholesale restructuring of the agency is not needed; common sense changes are. We in the medical technology industry will drive ahead to innovate and create products that meet unmet medical needs, such as cancer, arthritis, and heart disease. We need a well-run and market-driven regulatory process to make that happen.

Thank you.

Mr. McINTOSH. Thank you very much, Mr. Carroll. I appreciate your testimony.

Our final witness on this panel is Dr. Robert Larkin, who is an agriculture chemicals expert with Rohm and Haas Co.

Dr. Larkin, welcome.

Mr. LARKIN. Good morning, Mr. Chairman, and members of the special field hearing.

My name is Robert Larkin, and I am director of registration and regulatory affairs for the agricultural business of Rohm and Haas Co. I have responsibility for the registration of our agricultural chemicals worldwide.

Rohm and Haas, as you might know, is a multinational chemical company with headquarters in Philadelphia. Our worldwide sales in 1994 totaled over \$3.5 billion, of which agricultural chemicals makes up approximately 15 percent.

I want to thank you for the opportunity to address your committee this morning. Rohm and Haas Co. is not directly involved in the pharmaceuticals business, although a number of our products are used in the packaging or processing of food and pharmaceuticals and, therefore, are regulated by the Food and Drug Administration as indirect additives.

This morning, however, I want to focus my remarks to a very specific section of the Federal Food, Drug and Cosmetic Act that has great impact on our agricultural chemicals business. That section is section 409, which contains the so-called Delaney clause.

As you are undoubtedly aware, the Delaney clause was added to the Federal Food, Drug and Cosmetic Act almost 40 years ago in order to protect the Nation's consumers from the presence of cancer causing agents in processed foods.

The Delaney clause establishes a different standard for setting tolerances for pesticide residues of carcinogens in raw versus processed foods. This different standard leads to the nonsensical situation in which the same pesticide residue that is legal on grapes, a raw food, is illegal on raisins, considered a processed food.

The National Academy of Sciences coined the phrase the Delaney paradox to describe this disconnect in the statute.

The clause was enacted at a time when relatively little was known about the causes of cancer and when methods of analysis were able to detect chemicals in food at only the parts per thousand level. Although the enactment of the Delaney clause by Congress in 1958 might have been appropriate in light of science at that time, the passage of 40 years has made the Delaney clause an anachronism.

Instead of protecting the public health, the National Academy of Sciences concluded in their 1987 report that strict application of the Delaney clause might indeed increase the risks to the public from pesticide residues in their food supply.

You might ask why after 40 years the reform of the Delaney clause has suddenly become such an important issue. The reasons lie in recent legal actions. The first action occurred in 1992 when the Ninth Circuit Court in California ruled that EPA could no longer interpret the Delaney clause as having a de minimus exception.

Up to that point, EPA had allowed tolerances for pesticide residues in processed foods as long as those residues posed a dietary risk of less than one in 1,000,000 to consumers. A risk of less than one in 1,000,000 is considered as *de minimus* by EPA and is generally accepted as such by the scientific community.

The EPA had formally adopted this policy in response to the 1987 study by the National Academy of Sciences that concluded that this *de minimus* approach applied to both raw and processed foods would be more protective of the public health than strict application of the Delaney clause with its different standard for setting tolerances for processed and raw foods.

The court ruled that the Delaney clause did not allow for this *de minimus* exception, but rather required a zero standard for pesticide residues in processed foods and ordered EPA to revoke the tolerances in that particular action that could not meet this zero standard.

The second event occurred earlier this year when EPA and a number of environmental groups signed a consent decree to settle a legal action over the strict application of the Delaney clause.

As a result of this decree, EPA has agreed to review the application of the Delaney clause to almost 40 pesticides and over 100 tolerances over the next several years. This review could result in the revocation of a majority of these tolerances and end the use of these chemicals on the affected crops.

Without going into details, the uses that would be affected are not minor perturbations, but rather represent the loss of critical tools that the farmers of our country are relying on today to produce the wholesome, plentiful and affordable food supply that we enjoy in this country.

The impact of these tolerance revocations would be to drive up producer and consumer costs, decrease yield and quality of our growers' fruit and vegetable crops and increase consumer dependence on imported foods.

It is particularly frustrating to me to face these potential impacts over an issue that has no relation to public health. Both EPA and industry are in agreement that this issue is not related to health and safety, but rather it is an idiosyncrasy of the law. However, EPA is under court order and will have to move to revoke these tolerances whether it agrees with the court decision or not.

There is a solution to avoid this oncoming crisis, but action must be taken quickly. The solution is to adopt the recommendations of the National Academy of Sciences and to establish a single uniform food safety standard that applies to all food, whether raw or processed.

This approach has been adopted in H.R. 1627, the bill recently reported out of the DORFA subcommittee. This bill eliminates the forced distinction between raw and processed foods. Under section 408, as required in H.R. 1627, EPA can apply a single standard to all food.

There are other provisions of H.R. 1627 that will also enhance the safety of our food supply, but time does not permit me to go into the other provisions. However, while the Delaney clause is the centerpiece of H.R. 1627, all of these other provisions are an inte-

gral part of improving the laws governing pesticides in this country.

In conclusion, I would like to ask you for your support in implementing the conclusions of the National Academy of Sciences to establish a food standard for setting a tolerance for all food that would be more protective of the public health than the standards of the current Delaney paradox. You can do this through support of H.R. 1627.

Thank you.

[The prepared statement of Mr. Larkin follows:]

TESTIMONY OF

Robert H. Larkin, Ph. D.

Director Of Registration and Regulatory Affairs

Agricultural Chemicals

Rohm and Haas Company

Philadelphia, PA

Before the

Special Field Hearing

US House of Representatives

Norristown, PA

June 9, 1995

Good morning Mr. Chairman and members of this Special Field Hearing. My name is Robert Larkin, and I am Director of Registration and Regulatory Affairs for the Agricultural Chemicals Business of Rohm and Haas Company. I have responsibility for the registration of our agricultural chemicals worldwide. Rohm and Haas Company is a multinational chemical company with headquarters in Philadelphia. Our worldwide sales in 1994 totalled over 3.5 billion dollars of which agricultural chemicals made up approximately 15%.

I want to thank you for the opportunity to address your Committee this morning. Rohm and Haas Company is not directly involved in the pharmaceuticals business, although a number of our products are used in the packaging or processing of food and pharmaceuticals and therefore are regulated by the Food and Drug Administration as indirect additives. This morning, however, I want to focus my remarks to a very specific section of the Federal Food, Drug and Cosmetic Act that has great impact on our agricultural chemicals business. That section is Section 409 which contains the so-called "Delaney Clause".

As you are undoubtedly aware, the Delaney Clause was added to the Federal Food Drug and Cosmetic Act almost forty years ago in order to protect the nation's consumers from the presence of cancer-causing agents in processed foods. The Delaney Clause establishes a different standard for setting tolerances for pesticide residues of carcinogens in raw versus processed foods. This different standard leads to the nonsensical situation in which the same pesticide residue that is legal on grapes, a raw food, is illegal on raisins, considered a processed food. The National Academy of Sciences coined the phrase the "Delaney Paradox" to describe this disconnect in the statute. This Clause was enacted at a time when relatively little was known about the causes of cancer and when methods of analysis were able to detect chemicals in food at the part per thousand level. Although the enactment of the Delaney Clause by Congress in 1958 might have been appropriate in light of science at that time, the passage of forty years has made the Delaney Clause an anachronism. Instead of protecting the public health, the National Academy of Sciences concluded in their 1987 report that strict application of the Delaney Clause might indeed increase the risks to the public from pesticide residues in their food supply.

You might ask why, after forty years, the reform of the Delaney Clause has suddenly become such an important issue. The reasons lie in recent legal actions. The first action occurred in 1992 when the Ninth Circuit Court in California ruled that EPA could no longer interpret the Delaney Clause as having a *de minimus* exception. Up to that point EPA had allowed tolerances for pesticide residues in processed foods as long as those residues posed a dietary risk of less than one in a million to consumers. A risk of less than one in a million is considered as *de minimus* by EPA and is generally accepted as such by the scientific community. EPA had formally adopted this policy in response to the 1987 study by the National Academy of Sciences that concluded that this *de minimus* approach, applied to both raw and processed foods, would be more protective of the public health than strict application of the Delaney Clause with its different standard for setting tolerances for processed and raw foods. The Court ruled that the Delaney Clause did not allow for a *de minimus* exception but rather required a zero standard for pesticide residues in processed foods and ordered EPA to revoke the tolerances in that particular action that could not meet this zero standard.

The second event occurred earlier this year when EPA and a number of environmental groups signed a consent decree to settle a legal action over the strict application of the zero standard of the Delaney Clause. As a result of this decree, EPA has agreed to review the application of the Delaney Clause to almost 40 pesticides and over one hundred tolerances over the next several years. This review could result in the revocation of the majority of these tolerances and end the use of these chemicals on the affected crops.

Without going into details, the uses that would be affected are not minor perturbations but rather represent the loss of critical tools that the farmers of our

country are relying on today to produce the wholesome, plentiful and affordable food supply that we enjoy in this country. The impact of these tolerance revocations would be to drive up producer and consumer costs, decrease yield and quality of our growers' fruit and vegetable crops and increase consumer dependence on food imports. It is particularly frustrating to me to face these potential impacts over an issue that has no relation to public health. Both EPA and industry are in agreement that this issue is not related to health and safety but rather is an idiosyncrasy of the law. However, EPA is under court order and will have to move to revoke these tolerances whether it agrees with the court decision or not.

There is a solution to avoid this oncoming crisis, but action must be taken quickly before EPA initiates the revocation process as dictated by the consent decree. The solution is to adopt the recommendations of the National Academy of Sciences and to establish a single uniform safety standard that applies to all food - whether raw or processed. The NAS recommendations will both avoid the crisis and be more protective than the current Delaney Paradox. This approach has been adopted in HR 1627 - the bill recently reported out of the DORFA subcommittee. This bill eliminates the forced distinction between tolerances for raw commodities and processed foods under FFDCA and puts the authority for the establishment of tolerances for pesticide residues in all "food" under Section 408 thus removing processed foods from the authority of the Delaney Clause in Section 409. Under Section 408, EPA can apply a single *de minimus* or negligible risk standard to all food and find its way out of the Delaney Paradox.

In addition to creating a single negligible risk standard for all food, there are a number of other provisions in HR-1627 that will improve the food safety provisions of both FFDCA and FIFRA. Among these are provisions that

- . enhance the protection afforded infants and children as recommended by the NAS in its 1993 report on "Pesticides in the Diets of Infants and Children"
- . streamline the cancellation provisions under FIFRA that will allow EPA to take faster action, when warranted, against pesticide risks
- . provide for uniform national tolerances for pesticide residues
- . provide support for the registration of minor use pesticides - products that are vital to the continued production of a varied and wholesome food supply

Time does not permit me to go into detail on these other provisions. However, while Delaney reform is the centerpiece of HR-1627, all of these other provisions are an integral part of improving the laws governing pesticides in this country.

In conclusion, I would like to ask for your support in implementing the conclusions of the National Academy of Sciences to establish a uniform standard for setting tolerances for all food that will be more protective of the public health than the standards of the current Delaney Paradox through your support of HR 1627. It is imperative that this legislation be enacted in this session of Congress in order to insure Americans the continuation of a wholesome, plentiful and affordable food supply.

Mr. McINTOSH. Thank you very much, Dr. Larkin.

I hope later we can hear from Chairman Walker, who has worked a lot on the risk assessment bill.

I wanted to pursue a question with Dr. Molt on one of the two drugs he mentioned as an example. It is the one that Ms. Gladis had mentioned to treat Lou Gehrig's disease.

I think she was indicating in her testimony that there may now have to be another set of clinical trials for that drug. Is that the case? What is the status of that application with FDA?

Mr. MOLT. We have recently submitted to FDA a request for them to grant us a treatment IND. That is currently under review. We are optimistic that that will be approved, and then the drug will be made available under the treatment IND. We also will be filing a new drug application for the compound shortly, and FDA will work to approve it so it will receive full approval.

There is no requirement now for additional data before the drug is made available under the treatment IND, so we are optimistic that it will be available shortly under the treatment IND program.

Mr. McINTOSH. So currently it is not part of a treatment IND, or has that lapsed under the first approval?

Mr. MOLT. No. The drug is not approved in the United States.

Mr. McINTOSH. Did you not have one treatment IND?

Mr. MOLT. No. This is our first treatment IND. We have an IND under which some people are getting the drug in clinical trials. Based on positive results, we submitted a treatment IND, which will allow general access to the compound so that it will be available under a treatment IND.

Mr. McINTOSH. Would any patient whose doctor prescribes that be able to receive access, or is there a numerical limit?

Mr. MOLT. Again, it is somewhat limited by our production capabilities. There has to be some sort of system for allocating it.

Mr. McINTOSH. Do you receive reimbursement when—

Mr. MOLT. You are allowed to receive reimbursement under a treatment IND. Rhone-Poulenc Rorer is not going to seek reimbursement for its treatment IND.

Mr. McINTOSH. So the company will be providing that drug at its own expense until it is approved?

Mr. MOLT. That is correct.

Mr. McINTOSH. Thank you very much.

I will reserve the rest of the time for other members of the panel who have questions.

Mr. Fox, do you have any questions?

Mr. Fox. Thank you, Mr. Chairman.

I guess my first question would go to Dr. Blois, if I could. We appreciate all of you being here today and contributing your vast knowledge on how we can improve the system.

I was interested to hear your testimony with regard to the balance we need between purity of the drugs and also the need for being at the cutting edge of innovation and availability and access to our patients.

I would ask you a question dealing with when your goal is to refocus the agency to drug approval. Could you tell those of us who are not in the drug field but who are here as representatives of the people to try to move the process along, what are the different

phases as you go toward approval of the drugs? Phase I, II and III? Is that it? Can you tell us where the slow down seems to occur, Doctor?

Mr. BLOIS. Yes. The phases are really segments of the clinical development program, but let me state that before we start clinical development—that is, testing a drug in humans—we do a battery of animals studies to make sure that from animal studies the drug is safe at least in those tests and that there is some hope for efficacy—that is, that the drug will work.

Following completion of those studies, we submit to FDA an IND, which Dr. Molt referred to, which allows us to initiate human clinical studies. It is at that point that we start what we call phase I, which is really studying healthy volunteers as a rule, depending on the disease. It is usually in healthy volunteers to assess the safety and tolerability of the drug.

As we get information from that, if the drug is relatively safe or has an acceptable safety profile, we will expand the study of the drug into patient populations, relatively small and controlled at first, expanding as we get information about the drug. Those would be phase II studies.

We then expand into large scale phase III studies, which confirm the safety and efficacy in a relatively large population. By large population, I am talking about maybe up to 1,000 or 2,000 patients.

Following completion of those studies, we assemble all the information which we have gathered in preclinical, phase I, phase II and phase III, submit those data to FDA in the form of a new drug application, and FDA reviews and rules on those data.

Now, in terms of areas where there may be areas for improvement in the process, first off, I agree with what some of the other panelists have said. We do not want to see unsafe or ineffective drugs made available to the public. That, in my estimation, does not benefit anybody.

Mr. FOX. I do not think anybody wants that. You are right.

Mr. BLOIS. One of the areas that I think can be improved significantly is in the area of summary data, which I mentioned. In the original IND submission, there is a requirement for submission of more detailed data than perhaps is needed, recognizing that 9 out of 10 drugs that enter the IND phase never make it to the marketplace.

It would be reasonable to focus our effort on the amount of information necessary at that point in time, not to look at a product as if it were going to go fully through the approval process.

Again, at the time of submission of a new drug application, I think it is reasonable to submit summary data rather than all of the raw data that were gathered during a clinical investigation.

One other area that I think needs to be looked at, and it goes back to the present status of our scientific approach, is there is currently a requirement that we have two "pivotal" studies, two large confirmatory studies.

We would propose that the requirements be switched to one large study demonstrating safety and efficacy, followed by confirmatory data from other sources so that we do not have to do by rote two studies, but rather can look at innovative ways to confirm clinical results and again assure safety, efficacy and quality of a product.

Mr. FOX. You are suggesting instead of the two large studies one large study with confirmatory what?

Mr. BLOIS. Confirmatory data.

Mr. FOX. Data. Would that also include data from possibly other foreign studies?

Mr. BLOIS. Yes. We do as a rule now, as I mentioned, a global development program, which would have data from studies done in—

Mr. FOX. Are there not international standards by which all drugs must be made?

Mr. BLOIS. I am sorry?

Mr. FOX. Are there international standards by which drugs must be made?

Mr. BLOIS. Yes.

Mr. FOX. If I could ask that the chairman indulge me one more moment?

If I may ask a question as well to Dr. Molt, you were talking about incentives that we should provide for the FDA. What do you mean by that? What kind of incentives? Do you mean a new protocol or a new goal or what?

Mr. MOLT. I think right now the incentive system is one where there is if they do something wrong, they hear about it. If they hear something right, they do not. There is no retribution for no action.

The incentive system seems to encourage caution. No one is hauled before a Congress because they approved a drug. I think that that is something that we need to change. I think that there is a need to do something that rewards FDA for providing new therapies faster.

Mr. FOX. Encouraging the innovation?

Mr. MOLT. Exactly.

Mr. FOX. I have no further questions. Thank you.

Mr. MCINTOSH. Thank you very much, Mr. Fox.

I would like to now turn to Mr. Walker, who has to leave us shortly.

Mr. WALKER. Thank you, Mr. Chairman. I have just a couple of questions for this panel.

Primarily because all of you represent global companies doing business beyond the borders of this country, do you know of any other industrialized countries that have a more complicated drug approval process than what we have?

Is that a no? Do I understand the consensus of the panel is that amongst industrialized nations, we have the most complicated drug approval process in the world?

Mr. MOLT. I think it is the most demanding.

Mr. WALKER. The most demanding. That is not necessarily a bad thing in some people's opinion.

The question is whether or not we are over complicated to the point that we are not doing the right kind of thing in terms of the global marketplace. That is what I am trying to get at.

Mr. MOLT. I would say that we are overly cautious as a result of all the information that FDA seeks. I think that they are asking for maybe the right amount of information.

I agree with Dr. Blois that probably from one large study you can form a conclusion based on whether the benefit outweighs the risk. I think what FDA is excessively dwelling on is the risk aspect of the equation. I think other developed countries look at both sides of the equation.

Mr. WALKER. Do we have a better record overall than other countries in terms of preventing drug risk?

Mr. MOLT. There is no data that shows that, for instance, Europeans have any more adverse reactions than the United States population does.

Mr. WALKER. So in other words, our complicated system, in your view, is not leading to a system that is getting less risk in the system?

Mr. MOLT. That is what our problem is.

Mr. BLOIS. In response to your first question, I would say that the United States review system is different from the European systems in different ways. They are all complicated in many of the ways.

One of the primary differences is in the requirement for data submission and the process of reviewing raw data, reanalyzing manufacturer's data, auditing manufacturer's data. That is not present in most or in any European system. It is a much deeper review and assessment of the data than what is done in any European city.

Mr. WALKER. Is there any other nation at all comparable to the Delaney clause, Dr. Larkin?

Mr. LARKIN. No. The United States is unique in that aspect. It stands alone.

Mr. WALKER. It does make it kind of complicated in full competition.

How many of your companies are manufacturing a product outside this country which is unavailable in this country? Two. Two of the companies are manufacturing.

Were any of the products that you are manufacturing outside the country developed in this country?

Mr. POWELL. Our products are developed globally. We have approvals in other countries before the United States generally as a rule.

Mr. WALKER. What I am getting at is I know of a situation that is developing for Centocor, for example, in Chester County where from what I understand about our system, we in fact can research and develop the drug here, it can in fact be made available in other countries—in other words, be approved in another country—but then we cannot manufacture it here to sell in that other country unless it is available in this country. Is that correct? Is that where our law is right now?

Mr. CARROLL. There are exporting regulations, especially on the device side, so that it is easier to manufacture a device overseas and sell it overseas than it is to manufacture it here and export it.

In our case, we do manufacture here and export it, but we have—

Mr. WALKER. I am talking specifically now about drugs. Am I correct that under our laws if the drug is unavailable in this coun-

try, it cannot be manufactured here and sold in other countries. Is that right?

Mr. POWELL. That is correct. We cannot export drugs to other countries, even though they are approved in those countries, if they are not approved here.

Mr. WALKER. So if we develop something here that gets through a faster process in another country, you are almost forced to take that manufacturing out of this country in order to offer that product in the country where it is approved? Is that right?

Mr. POWELL. That is correct. When you investigate the drug in another country, it is very difficult to export it as well. Quite often we are forced to manufacture even clinical supplies for drug studies outside the country.

Mr. WALKER. So chances are once you have manufactured a product in another country, even once it gets approved here the likelihood is you will continue to manufacture that product there and ship it back here. We kind of lose the manufacturer of that drug forever by that process. Is that correct?

Mr. CARROLL. That is the case for our drug, Mr. Walker.

Mr. CLINGER. Would the chairman yield for just a minute?

Mr. WALKER. Sure. I would be happy to.

Mr. CLINGER. Just a question. Does that apply to pesticides as well, Dr. Larkin?

Mr. LARKIN. It is not quite as black and white with pesticides, but there are such stringent regulations about exporting pesticides that are not registered in this country.

I do not think we, Rohm and Haas, would ever build another manufacturing facility in the United States because, similar to the drug industry, we almost always get registrations overseas first and, therefore, locate our manufacturing facilities overseas first.

Mr. WALKER. One last point. Is there any nation in the world that you would regard as having a regulatory process that you think is a good model for us to look at as we are trying to determine what direction we should go?

Mr. POWELL. I would propose that the British system is probably one you would want to look at.

Mr. WALKER. The British system?

Mr. POWELL. Yes. It utilizes outside experts. It utilizes summary data. It does not review all the raw data, as does the United States. I think it has a lot of the benefits of the things we are proposing.

Mr. FOX. Is there a general agreement on the panel that that is probably the better model?

Mr. WALKER. Thank you, Mr. Chairman. That was the extent of my questions.

Mr. MCINTOSH. I wanted to have a followup on that one. Would you think that we would be adequately protected here in this country if we acknowledged their approvals and just reciprocally said if it is approved in Great Britain it could be marketed here in the United States?

Mr. POWELL. I am not so sure I would go quite that far. I think what should happen, though, is FDA should establish what the standards are. There should be a harmonization of those standards throughout the world so that that eventually can happen.

Certainly there are some countries I think that you could propose that we could accept approval of those countries as *prima facie* evidence that it should be approved in the United States.

Mr. MCINTOSH. But only *prima facie* evidence and not conclusive?

Mr. POWELL. Like I say, I think that FDA has the responsibility to assure themselves that the country which is reviewing the data has reviewed to their standards. I think the United Kingdom and Germany and a lot of countries in Europe would meet those standards today.

Mr. MCINTOSH. Any other views on the reciprocity issue?

Mr. MOLT. There are some problems with that solution. Some diseases are somewhat different in Europe than they are in the United States, especially infectious diseases and things like that. There would be a problem with some sort of blanket statement that European acceptance would warrant United States acceptance.

Mr. MCINTOSH. So it may not be as effective here as it would there?

Mr. MOLT. It could be a different strain of organism that is causing the disease. It might not work as well here. That is correct.

Mr. MCINTOSH. How about on the safety side? Would you anticipate any difference there?

Mr. MOLT. Again, it depends. I think it is more on the efficacy side than the safety side. I think that safety probably is generally—except in some European countries, yes.

In Japan, for instance, there are different metabolisms and things like that that may cause a different safety profile as well. Looking at other areas for approvals may not hold the United States both in efficacy and safety.

Mr. PETERSON. I know the Japanese claim they need to run the tests over there on that basis.

Mr. MCINTOSH. Thank you.

Mr. PETERSON. Dr. Molt, you said that you thought that the FDA should have more incentive base in the system. Do you have a solution, or do you have a proposal other than adopting something like the British? Has anybody thought that through?

Mr. MOLT. No. I mean, to change the incentive system at FDA is a hard job. I think that we may be able to do it through legislation. I think that—

Mr. PETERSON. Excuse me. Do you think you could look at in the proposal the reinvention of the MDA proposal? Have you seen that? Have you seen that reinvention of the MDA proposal?

Mr. MOLT. Yes.

Mr. PETERSON. Do you think that does it?

Mr. MOLT. I think there are components of it that would help. One thing that I mentioned when I was closing was that I think that congressional oversight might want to be looked at in terms of what we or what the public through Congress does to FDA, how we view them, what their incentives are.

Again, I think that traditionally FDA is called before Congress to be looking at decisions based on approving the drug where the risk was perceived to be too high. They are extremely cautious not to do that.

Mr. PETERSON. I am just curious. How do we change that? I do not think you are going to change Congress' attitude. They do not get riled up unless somebody riles them up a lot of times.

Mr. MOLT. I agree that changing FDA might be easier to change than Congress.

Mr. PETERSON. Dr. Powell?

Mr. POWELL. I would like to comment. I have thought about that a bit. In my testimony I proposed that there be an oversight committee to make sure that the FDA is following the mission statement that Congress would pass.

That oversight commission would have the authority and the power to recommend policy and personnel changes within the agency. I would think that they could also be given the power to award bonuses for good performance against the mission. The moneys for those bonuses could come from the user fees.

It seems to me there are all kinds of opportunities to change the incentive system so that it is more like a commercially incentive system. People work for a reward, and they avoid punishment. It seems to me that that would work.

Mr. PETERSON. My question is has anybody put that in writing? Is there any kind of proposal that is out there that we could look at? Can you put that in writing for us?

Mr. MOLT. We could, sure. I think we have been thinking along those lines.

It is difficult. I did not want to be glib before, but it really is a difficult thing to try to put true incentives on that kind of system because by nature it should be a cautious system. As David Blois said, we do not want to approve drugs that are not safe, so it is difficult.

Mr. PETERSON. Dr. Larkin, on the Delaney item, I serve on the Ag Committee, but I do not serve on I think it is the DORFA subcommittee dealing with this. Does that bill fairly well have everyone's support now? Is EPA behind it?

Mr. LARKIN. EPA has problems with certain aspects of it. I think—

Mr. PETERSON. On the Delaney part of it?

Mr. LARKIN. No, not on the Delaney part. I think there is unanimity over changing Delaney.

Mr. PETERSON. How about within the environmental community? Are some of the radical environmentalists on board finally or not?

Mr. LARKIN. I would say that the middle of the road environmentalists are probably on board. I would say that there are fringe elements that are not.

It becomes somewhat of a trading act in that you can fix Delaney, but what will you give us in return? That is really where we are at right now.

Mr. PETERSON. We keep running into these different groups that want to do things that I do not think we can accomplish. There are these people that claim that they want zero risk and that they are never to blame and that they are always the victim.

Is there some way we could have some Government programs so that we could give them this and then charge three or four times more than what we charge everybody else if that is what they want and then use that money to get at some of these problems?

It is very frustrating trying to deal with it. Generally everybody is on board except for just a few fringe groups.

As I understand, they are going to put this in the farm bill. Is that what we are planning on doing?

Mr. LARKIN. Excuse me?

Mr. PETERSON. I think we are going to try to put this in the farm bill, as far as I know.

Mr. LARKIN. I think we hope it stays out of the farm bill because that complicates things further. We would rather handle it stand alone and not get it mixed up with trading subsidies for Delaney clause changes, etc.

Mr. PETERSON. I see. I have heard some rumors that they might put it in there. I think it maybe would make it easier to do it, but we will just have to see what happens.

Thank you, Mr. Chairman.

Mr. MCINTOSH. Thank you, Mr. Peterson.

Chairman Clinger.

Mr. CLINGER. Just a couple of questions. I am reading a book called *Thickening of Government*, which suggests that in any bureaucracy there is an inevitability about over time new levels of control. New bureaucracies are built in. In other words, the Government almost inevitably grows in scope and jurisdiction.

Given your experience in dealing with FDA over the years and seeing the fact that we have now gone from 6 years to 10 to 12 years in terms of time, how much of that is due to what this author suggests is just the inevitable thickening of Government and the adding of additional layers of review and approval? And, how much is it attributable to improvement of science, the requirement that things become more complex, more difficult to determine? Can you quantify the differences?

Mr. BLOIS. I can start to quantify. I think that there are times in the process that are attributable both to the manufacturer and to the agency requirements.

We have looked at the time for just starting trials, and we think we can improve 2 to 3 months in that framework. I think if you look at the other end of the spectrum in terms of the review process, and that is a regulatory requirement, we can improve that by some several months.

If we look at the approval process, I think that the timeframes are coming down significantly. We talked about 19 months earlier. The user fee legislation would have action in 12 months for standard new drugs and 6 months for priority drugs. We can take that 19 months down perhaps to 12 months at max.

In terms of the manufacturer's time, if we go back to one of the comments I made about the two pivotal trials and cut that to one pivotal trial plus other data, I think we can save some time there.

On the other hand, though, I think we need to understand the science and the types of studies that we are doing. The disease processes we are looking at are chronic diseases now. We are looking at long term, and that by its nature requires longer periods of study.

I think there are timeframes that could be saved in the regulatory process, but I think we also would need to recognize that what we are as an industry doing and the types of diseases we are

commonly looking at are different and require long periods of study.

Mr. CLINGER. Somebody recommended using outside experts to do some of this. Would that help?

Mr. POWELL. I think it would. One of the problems the FDA has is it spends a lot of time verifying and documenting data that is submitted for new drug applications, which are the No. 1 priority obviously even of the agency.

As a result, they do not have the time to devote to working with the manufacturers during the development of the drugs. Often times development will be delayed just for the simple reason we cannot get meetings with the FDA in a timely fashion to discuss and agree on programs.

I think that the use of outside sources would help alleviate that problem, reducing the amount of data verification that the FDA reviewers have to do and would allow them to have more time to work with the manufacturer and speedup the drug development process in general.

Mr. CLINGER. Have you sensed in recent years or months or whatever, that the FDA has become more responsive to these kinds of concerns?

Mr. POWELL. Yes, I think it has, but it is severely constrained with resources. They have the same problem everybody else has. The resources have to be assigned to the jobs that are primary. If the process is so complex that they spend a lot of time reviewing, they do not have time for the other things.

Mr. BLOIS. I would just like to add that the user fee legislation which came into place in 1992 I think has produced a noticeable change. It has now made available the resources for FDA to have in place to review applications when they are received, and we have seen significant improvement in the overall process and a focus on the timeliness of the review.

That has been something that has been a very positive effect, and I think Dr. Lumpkin may reflect on that later on.

Mr. MCINTOSH. If the gentleman would yield?

Mr. CLINGER. Yes.

Mr. MCINTOSH. Is that also the case with some of the new biotech companies? Do you find that additional resources have speeded the review?

Mr. CARROLL. Our president is a firm believer in the user fee if it is allocated where it is supposed to be. He has cited the fact that the speedier approval of our drug was a direct result of the user fee.

Mr. CLINGER. I just have one final question, and that has to do with where the disease is terminal, where there are no cures for these diseases such as we heard testimony here today.

What are the down sides to just approving it? Why should we hold up any potential help in that area? Why would we interpose any time between the availability of that drug, unproven as it may be?

Given the fact that the disease we are dealing with is terminal anyway, is there not some advantage to allowing that to go forward? What is the down side of not allowing it to go forward?

Mr. POWELL. There are some down sides, particularly in terminal diseases where you expect the patient to die if indeed you decrease their lifespan with the drug. It would be difficult. You have to at least guarantee that you are not hurting the patient before you—

Mr. CLINGER. First do no harm?

Mr. POWELL. First do no harm. I think that is important. Nevertheless, I think that there could be and I think there is considerably less conservatism for treatments of terminal diseases. I think the FDA for the most part should be commended for their efforts in this area.

Mr. MCINTOSH. In that case then you would argue that you only need to test for safety and not for efficacy?

Mr. POWELL. If there is no other treatment, yes.

Mr. MCINTOSH. Thank you. Thank you all.

Mr. Tate, did you have any questions?

Mr. Fox, you have an additional question?

Mr. FOX. Yes. Following the chairman's question previously I guess to Dr. Powell on the time period, I think you were talking about the 10 or 12 years some drugs might take.

Can you quantify the number of years you thought how much was for good science and how much was really for maybe over regulation?

Mr. POWELL. I have never thought about it, but roughly I would think we could reduce a couple of years off of the total development time just by improving the process. I could not give you the exact detail.

Mr. FOX. I understand. Going back to your testimony on page 4, how would you, briefly if you can, facilitate the timeliness of the speed process? We have heard good testimony regarding the incentives. What else would you do to speed it up?

Mr. POWELL. As I mentioned and as Dr. Blois pointed out, if you can focus the resources on the issue of making drugs available rather than focusing those resources on compliance and on data verification, that alone would help speedup the process considerably.

Mr. FOX. I have no further questions, Mr. Chairman.

Mr. MCINTOSH. Thank you very much, Mr. Fox.

Thank you all for participating today. We appreciate it, and we appreciate your written testimony. There may be a few additional questions that come up throughout the rest of the day.

If you all would not mind, if we could submit those to you if there is any additional information we need? We will hold open the record for that purpose.

Also let me urge you that if there are additional things you wanted to put in the record that you were not able to as part of your verbal testimony, please make sure you submit those to us. We will include them in the record.

Thank you.

We will move now to the third panel. Dr. Lumpkin, if you would come forward?

One of the things we have asked is that the agencies, when we are going through some of these regulatory issues, attend and participate in these hearings, but also attend and listen to some of the testimony.

Our next witness is a representative from the Food and Drug Administration, Dr. Mike Lumpkin. Actually, Mike, I will let you give your title so I do not get it incorrectly. I appreciate you coming up here from Washington with us today. As you can expect, there are a lot of questions that we will have for you.

If you could give us your opening statement? Before we do that, let us swear you in.

[Witness sworn.]

Mr. McINTOSH. Let the record show the witness answered in the affirmative.

Dr. Lumpkin.

STATEMENTS OF DR. MURRAY M. LUMPKIN, DEPUTY DIRECTOR FOR REVIEW MANAGEMENT, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. GEORGE ROSS FISHER, TRUSTEE (PHILADELPHIA), PENNSYLVANIA MEDICAL SOCIETY; DR. ROBERT B. SKLAROFF, MEDICAL COLLEGE HOSPITAL-ELKINS PARK; DR. MICHAEL R. SPERLING, CHIEF OF MEDICAL/SURGICAL PROGRAM, COMPREHENSIVE EPILEPSY CENTER, GRADUATE HOSPITAL; DR. JACK CIONCI, CHAIR, MONTGOMERY COUNTY AIDS TASK FORCE; DONALD JUNGKIND, THOMAS JEFFERSON UNIVERSITY; DR. DAVID O. GINSBERG, PRESIDENT, CONCORDE CLINICAL RESEARCH, INC.; JOHN BOEHRINGER, PRESIDENT, BOEHRINGER LABORATORIES; AND BARBARA DELUCA, EXECUTIVE DIRECTOR, LINDA CREED BREAST CANCER FOUNDATION

Dr. LUMPKIN. Thank you, Mr. Chairman. As a way of introduction to the committee, since I have not had the opportunity of appearing before you, let me first tell you that I am a physician, and I am not a political appointee at the FDA.

I actually have had a bit of I think a very fortunate career as far as drug development goes in that I have only been with the FDA for approximately 5 years. I came to the FDA in 1989 as the director of the division of anti-infectious drug products. This is the division that deals with antibiotics. After 3 years in that position, I was asked to assume my present position at the FDA, which is the deputy director of the Center for Drug Evaluation and Research.

Prior to my time at the FDA, I was employed by Abbott Laboratories in Chicago, IL, and I was head of one of their antimicrobial development programs that led to the worldwide registration of one of their new antibiotics.

Prior to that I was a practicing physician. I was head of the pediatric infectious disease department at East Tennessee Children's Hospital in Knoxville, TN. I did my training at the Mayo Clinic, and I was a Fulbright Fellow at the University of London.

As I say, I think I have had a very fortunate career in that I have seen drug development from the practicing physician, from the patient, from the pharmaceutical industry, and now I am having the opportunity of seeing it inside a regulatory agency.

I really am very pleased to be here today to have this opportunity to discuss with you and with the people here in Norristown

a lot of the important issues that you have already begun to hear about today from many of the witnesses who have already testified.

One of the points that I think people have brought up is this issue of a mission statement and trying to define what the FDA's mission is. I can tell you that as far as the Center for Drugs is concerned, in 1995 we realized that our statutory mission is to protect and promote the public health of all Americans that have to do with products that are under our jurisdiction.

I think we have to realize that this is really a multifaceted mission when you begin to think about it. It is not a simple mission, and it is not one that one can hone down very easily.

Clearly this involves promoting public health. It involves insuring that drugs are proven safe and effective before they are available for general marketing in our country. Clearly it means that we assure that valiant, thorough information is available to healthcare practitioners and to consumers to help assure that they make truly informed decisions on the appropriate use of pharmaceutical products.

I think clearly it means that we have to have in place a process whereby drugs that have good scientific data that demonstrate their safety and effectiveness become available to Americans as promptly as possible. This is a mission that clearly is as absolutely vital today as it was 90 years ago when the first Food and Drug Act was approved.

I think when you talk about standards of efficacy and safety, this is not something that only benefits consumers. I think we have to realize that this also benefits the medical profession, and it benefits industry because it gives credibility to our pharmaceutical industry, and it is an industry that deserves the credibility that it has in the world market today. It heightens competitiveness of our product because people know that products that are available in the United States have undergone very stringent safety and efficacy testing.

I think the world has realized that indeed this general approach to the overview and to the development of drugs has value because I think we see in most modern countries, as people were pointing out today, the basic standards are fairly similar. What is at issue here is the process for how one gets through the independent evaluation of the data that people have.

Mr. Chairman, these are really very, very exciting times for those of us at the Center for Drugs. As you are aware, we have a new management team in at the Center for Drugs. Dr. Woodcock, who is our Center director, and I have been in our positions for about a year and a half.

I think when people really begin to look at the recent data on the performance of what our Center has done and we begin to separate some of the rhetoric from the reality of what is going on today compared to what went on in past years, to paraphrase a commercial that is popular now, I think at least for the Center for Drugs you will find that this is not your parents' FDA.

Having said that and having said that with pride in what I think we have accomplished in the year and a half that the new management team has been there, I will be very clear and forthright in saying that we still have a long way to go, but we have a process

that has been negotiated with Congress. It has been negotiated with the pharmaceutical industry. I think it is a process that we at the Center are very committed to. I want to talk about that for just a few minutes.

That process is the Prescription Drug User Fee Act. As many of you know and it has already been talked about today, the Prescription Drug User Fee Act, as far as I am concerned, is an act that in all of my experience, both on the industrial side and on the regulatory side, has been the first real catalyst for culture change at the Center for Drugs because for the first time it has made very real to our reviewers and to our management that accountability is something that matters.

It is not only good decisionmaking, but it is good decisionmaking in a timely manner and that people will be held accountable for that. I think that was the idea when people from FDA, people from the pharmaceutical industry and those of you here in Congress put together the basic premise for the Prescription Drug User Fee Act.

Now as you are well aware, this is an act that started in 1992. It has a 5-year implementation to it. It ends in 1997. It has a sunset provision. If Congress does not re-up it in 1997, it will go out of existence at that point in time.

During this 5-year period, there are interim goals that were mandated in the exchange of letters between the commissioner and the Congress when this act was put into place. I can tell you and it is public record. We have our records that are available on a monthly basis. We have met all of the interim goals that were set in that program.

I think we are already beginning to see the effects of the program and having a process by which you have an expedited, efficient review process such that when you have an application that has good scientific data in it that if it can be reviewed in a timely manner, then obviously it is going to be approved in a timely manner.

If I could have the first chart there?

[Chart.]

Dr. LUMPKIN. These are the same kind of numbers that I think some of the representatives from industry were just talking about. If you look back in 1992 at the beginning of this program, the median time for drug approval for all NDA's at the Center for Drugs was around 26.7 months. Last year, when you look at all NDA's that were approved, the median time was 19 months.

If you look at those applications that came in under the user fee program, the median time for their approval was 13.5 months. For those user fee applications that we call priority applications—these indeed were for drugs that were for lifesaving illnesses—their meeting an approval time was 10.4 months.

Clearly this has not yet reached the goals that were set in the user fee program, but those goals are not in place until 1997. There are interim goals on the percentages of applications that have to meet the performance goals in there, and we have met those percentages.

I think what you will begin to see and what the whole idea behind the user fee program was is that because we want to develop

an efficient review process, we will then begin to see decreases in approval time.

Mr. Chairman, I also want to take just a couple of minutes to talk a little bit about some of the other issues that witnesses have already brought up today because I think these are clearly very, very important issues that we need to talk about.

That is not just using the user fee program as a way of getting the overall process under control, but also realizing that the overall process does not always meet the needs of every individual and the needs of every disease.

I think we at the agency have instituted several programs that have been highlighted already to try to meet those other contingencies that are clearly just as important as the overall performance of the FDA Center for Drugs.

One is the expedited availability. You have heard already about the fast track procedures for life threatening illnesses. You have heard about the accelerated approval regulations that went into effect in 1992. Under these new procedures, we have been able, for example, to approve AZT in three and a half months. We have been able to approve some of the new drugs that are related to AIDS such as ddI prior to their approval in the United Kingdom, Germany or Japan.

These we think are some very good ways to begin to deal. It might not be the final answer, but clearly it is an improvement over what the Center has had in the past. We are coming to grips with the fact that with life threatening illnesses it is a different situation than for just another drug to treat strep throat.

The other thing that I wanted to spend just a couple of minutes on to talk about were the kinds of situations that many of the early witnesses were talking about where you have situations where drugs are being developed and people are believing that indeed we are beginning to get some early data that these things are effective.

The issue then in life threatening illnesses is how to afford access for patients that need this while at the same time not destroying your ability as a community to find out the ultimate truth about the drug, whether indeed for the great majority of people who have that disease the drug is going to be safe and effective.

I think under our expanded access programs, be it treatment IND's, be it parallel track, be it emergency IND's, in the last 6 years we have afforded access to over 75,000 Americans who needed and wanted access to drugs that were still under development. They were still undergoing the clinical trials development. These were people who were not in the clinical trials.

I think we are very sensitive to this. We are trying to be very sensitive to this, and we are willing to work. We have shown I think that we are willing to work with the communities to come up with programs that will afford access in these situations, but at the same time try to protect us as a community, protect our ability to find out the ultimate truth of these drugs in our clinical trials program.

In conclusion, Mr. Chairman, I just want to say, as you pointed out, there are a lot of other things that are being discussed right now. That is part of actually the tremendous fun of being at the Center for Drugs right now.

The administration has proposed various reinvention types of ideas that have already been discussed. We are very active in what is called the International Conference on Harmonization.

This is a process by which the regulatory authorities for drugs in the United States, in the European Union and in Japan, in conjunction with the pharmaceutical manufacturers in those three areas, work together in an organized process to try to harmonize as much as we can on the standards, not only the clinical standards, but the manufacturing standards, the animal preclinical testing standards, to try to come up with as best we can dealing with some of the time elements in the development process that have already been talked about.

In conclusion, Mr. Chairman, I would just like to say that this is obviously an era of change. There is a lot going on in the healthcare system of which all of us are aware, there is a lot going on in the pharmaceutical industry of which all of us are aware, and there is a lot going on at the FDA of which I am trying to make more and more of us aware because I think it is important that what we are trying to accomplish there is discussed in our open political debate situation.

I think in the end it is FDA's independence that gives American consumers confidence in our agency's decisions. I think that now our challenge is to continue to build a track record on efficiency that will give Americans a confidence in the agency's processes.

I thank you for your time, and I am happy to answer any questions that you happen to have.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Lumpkin follows:]



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Public Health Service

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STATEMENT BY
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SUBCOMMITTEE ON ECONOMIC GROWTH,
NATURAL RESOURCES, AND REGULATORY AFFAIRS
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT
U.S. HOUSE OF REPRESENTATIVES
NORRISTOWN, PENNSYLVANIA

JUNE 9, 1995

FOR RELEASE ONLY UPON DELIVERY

I am pleased to be here today to have this opportunity to discuss important issues concerning the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). The FDA's primary mission is to protect and promote the public health of all Americans. Promoting public health means ensuring that drugs are safe and effective, and that information is available to health care practitioners and consumers to help assure appropriate use of pharmaceutical products. It also means making every effort to assure that drugs that have scientific data demonstrating their safety and effectiveness become available promptly.

Under our law, drug companies are required to test drugs for safety and effectiveness. Once that testing is complete, they submit a new drug application to one of two centers at FDA. CDER is responsible for ensuring the safety and effectiveness of drugs made from chemical substances. The Center for Biologics Evaluation and Research (CBER) is responsible for the regulation of biological products. Traditionally, biological products included vaccines, therapeutic sera, allergenic products, and blood and blood products. In recent years, biologicals have come to include products produced by recombinant DNA technology, monoclonal antibodies, and certain types of gene therapy.

The FDA's consumer protection mission is absolutely vital--as vital today as it was the day the Pure Food and Drug Act was passed 90 years ago. The assurance that FDA is there, every day, doing its job, is fundamental to what the American public knows and expects as public health protection. The standards for safety and effectiveness of drugs not only protect consumers, but also give credibility to industry and bolster consumer confidence in its products. The world has recognized the benefits of these standards; most modern countries, alone and in groups like the European Union, have developed principles of drug development and evaluation that are very similar to the ones we have.

But high standards alone are not enough. Promoting public health also means making timely decisions about the safety and effectiveness of important new drugs. During recent years the Agency has made significant strides in making important drugs available to people in need more quickly. It is time to dispel the myth that the United States lags behind other nations. The truth is that today the United States often outperforms other countries in terms of product availability. This is particularly the case for products that either provide treatment for life-threatening diseases for which there is no other therapy or offer important therapeutic gains over existing U.S. products for any

disease.

There are four separate initiatives we have undertaken to accomplish twin goals of protecting the public and promoting the rapid availability of effective drugs. These four initiatives, along with ongoing management efforts to streamline and improve the drug review process, will guarantee that safe and effective therapies continue to be available as rapidly as possible. I would like to tell you about each of these initiatives.

EXPEDITING AVAILABILITY

First, years ago FDA established a fast-track procedure for drugs representing real gains, including breakthrough drugs--drugs to treat persons with life-threatening and severely debilitating illnesses, and for which there is no other treatment available, as well as other drugs that have significant advantages over drugs already on the market. The Agency has long worked very closely with companies throughout the drug development and review period, even before anything is submitted to the Agency, so as not to waste any precious time. Many drugs have been made rapidly available because of these steps. A conspicuous example came in 1987, when FDA reviewed and approved AZT, the first drug

for the treatment of AIDS, in 3-1/2 months. Today, AIDS and cancer drugs for which adequate data are presented typically are reviewed and approved in a year or less, sometimes much less, and other important drugs are also often approved in this amount of time.

In December 1992, FDA established a program, called "accelerated approval," which allows approval of drugs for serious or life-threatening illness based on the drug's effect on a surrogate endpoint. A surrogate endpoint is an effect that is not a clinical benefit itself but is reasonably likely to correspond to or predict a clinical benefit. For example, under this program the AIDS drug d4T was approved on the basis of data that the drug raises T-Cell counts. While there is reason to believe that increased T-Cell counts in an AIDS patient will prolong life, there was no actual evidence that d4T produced a clinical benefit such as prolonging life. Nevertheless, the Agency approved d4T less than six months after the application was submitted on the condition that studies demonstrating a clinical benefit be completed after approval. When approval is based on a surrogate endpoint under the accelerated approval rule, the sponsor is required to conduct postmarketing studies to verify and describe the drug's clinical benefit.

In recent years, d4T and many other breakthrough drugs have been approved in the United States before they were approved in other countries such as the United Kingdom, Germany, and Japan.

EXPANDING ACCESS

Second, over the past ten years FDA has formalized and implemented a variety of programs to make promising drugs that are being tested but have not been approved available to patients. Under FDA's "Treatment IND" provision, patients for whom there is no satisfactory alternative treatment receive pre-approval access to a promising drug after clinical trials have shown that it may be effective and does not have unreasonable risks to the patient. Treatment is given under simplified protocols that collect important safety information. Similarly, our parallel track program allows HIV-infected patients who are unable to join a controlled trial access to the experimental drugs. We also allow other experimental drugs to be made available under an emergency or single patient IND for patients who are in need of a drug but do not meet protocol criteria.

As a result of these programs, since 1987 more than 75,000 patients, not in formal clinical trials, have received access to promising new drugs while the drugs were being studied.

PRESCRIPTION DRUG USER FEE PROGRAM

The third program is one that is particularly important to the health of the drug industry and it is the one for which Congress deserves substantial credit. I am referring to the program established under the Prescription Drug User Fee Act of 1992 (PDUFA). The bill was endorsed and agreed to by the two lead trade associations for the drug industry--the Pharmaceutical Manufacturers Association, now the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization. It was passed unanimously by both the House of Representatives and the Senate and signed into law by President Bush.

The theory of the bill was that FDA would be able to review drugs in a timely manner if it had sufficient resources. An FDA-industry work group studied FDA's programs and identified the

necessary resource levels. The bill was drafted so that the resources would be additive to the FY 1992 existing resource base.

Drug approval data at the time suggested that there was considerable room for improvement in review times. Between 1970 and 1989, FDA approval times consistently averaged between 2 and 3 years. In those years, FDA approval typically took about 1 to 2 years longer than the fastest European countries. There were improvements in the early 1990's as the median approval times fell below 24 months and as average times dropped toward 2 years.

It was clear that if PDUFA worked as anticipated there would be enormous benefits to the prescription drug industry. An often cited study by Dr. Lasagna at Tufts, indicates that a one year delay in a drug approval costs the sponsor 19 million in 1987 dollars, which translates into 25 million in 1995 dollars. [Vol.X, Journal of Health Economics, pg. 107, 128 (1991)]

Under the user fee legislation FDA agreed to very ambitious goals with respect to drug reviews, review times that would have been impossible to achieve only a few years ago. By 1997, once the legislation is fully implemented, the goals provide that the

Agency will make decisions on 90 percent of drug applications within 12 months. Medically important drugs will be reviewed twice as quickly, with reviews on 90 percent of those products to be completed within 6 months.

As a result, by 1997 the U.S. drug review process will be as fast as that of any country in the world with a developed drug approval process. This will be accomplished without diminishing the public health protections FDA traditionally has maintained.

Significant progress already has been made. During the first 2 years of the user fee program, all drug approval times have fallen significantly. As expected, shortened review times have led to shortened approval times. In 1994, the average time for approving prescription drugs that are new chemicals was 19.7 months, down 24 percent from 1992, and the median time was 17.5 months, down 33 percent from 1992. Priority drugs, drugs that represent a significant advance over the drugs that already are available, were approved even more quickly, the median time being 15 months, down 42 percent since 1992.

The data are even more impressive for drugs approved in 1994 that were reviewed under the user fee program. The median review time

for user fee submissions approved in 1994 was 13.5 months. The median approval time for priority drugs was 10.4 months. (See attached charts)

The user fee program is changing the culture of the Agency. Although the drug review deadlines are ambitious, they are realistic. We are all benefitting. FDA reviewers are beginning to get the resources they need to review drug applications faster and still maintain a high standard to ensure safety and effectiveness. The drug companies benefit from getting their products on the market earlier in the United States, which helps get the products approved abroad. And, most importantly, the patients who might benefit from use of a drug have quicker access to them.

REINVENTING REGULATION OF DRUGS

The fourth initiative encompasses the reforms recently announced by the Clinton Administration as part of President Clinton and Vice President Gore's National Performance Review. In April we proposed five significant changes for regulation of drugs and

biologics. Additional changes will be announced in the near future.

First, drug companies are frustrated that it often takes months to get FDA approval for a manufacturing supplement to their original product applications--even for minor changes in the content or manufacturing process of a drug or biologic. These could be changes in the product itself, such as the use of a new color additive, or changes in the manufacturing process, such as the use of a new machine. We believe there are many such changes that do not need to be reviewed by the Agency or which should require only brief notice to the Agency. FDA is preparing guidance to the industry for when a manufacturing supplement will or will not have to be submitted to FDA. Our guiding principle is to require FDA review of manufacturing changes only when the change raises issues pertaining to safety or effectiveness. We will not need to review the change if it does not raise significant safety or efficacy issues. We intend to issue guidance for most products sold in tablet form by the end of this year. A similar publication covering other dosage forms, including controlled release drugs, liquids, and semi-solids will be completed by the end of 1996, which will eliminate our current review of more than 800 supplemental applications.

We also looked at environmental requirements that pose significant costs for drug and biologic manufacturers in getting a new drug approved--complying with the National Environmental Policy Act (NEPA). Pursuant to NEPA, the FDA for many years has required pharmaceutical companies to submit with new drug applications a formal environmental assessment of the impact of approving the product. In virtually all cases, there has been little or no significant impact on the environment. Yet these evaluations each cost tens of thousands of dollars. In fact, some companies estimate the cost to be several hundred thousand dollars.

We intend to increase the number of categorical exclusions to the requirements to prepare these assessments that will eliminate the need for them, except in rare cases. This will free millions of dollars of industry resources to be applied to other avenues of drug development.

We also announced reforms in the regulation of antibiotics and insulin, which have been subject to special controls since the 1940's. Today, these products can and should be regulated like other drugs, and we will be asking Congress to repeal the special

requirements for those products. This change will eliminate about 700 pages of unnecessary regulations from the Code of Federal Regulations.

Finally, I would like to mention the issue of exports of unapproved drugs. I want to emphasize that this is not an issue on which the Agency has any particular expertise. In fact there is a strong argument to be made that this is not really an issue of public health since products not approved in the United States inevitably get to other countries, whether we allow their export or not. Instead, the issue turns on the extent to which we, as a country, are comfortable with permitting the export of products which cannot be sold here, but which are sold in other countries.

Current law allows drugs to be exported to 21 industrial countries identified in the Federal Food, Drug, and Cosmetic Act, if the drug is under investigation (IND) in the United States, the foreign country approves of the shipment, and certain other conditions are met. Export of unapproved drugs to other countries is not permitted by law.

The Administration proposes to reduce administrative burdens on the export of drugs to the 21 countries, and in particular to eliminate the requirement that there be an IND in the United

States before the product may be exported to a foreign country.

In addition, the Administration proposes to work with Congress on changes in the current law based on an examination of whether to amend the present list of 21 countries, and whether to adopt other changes.

CONCLUSION

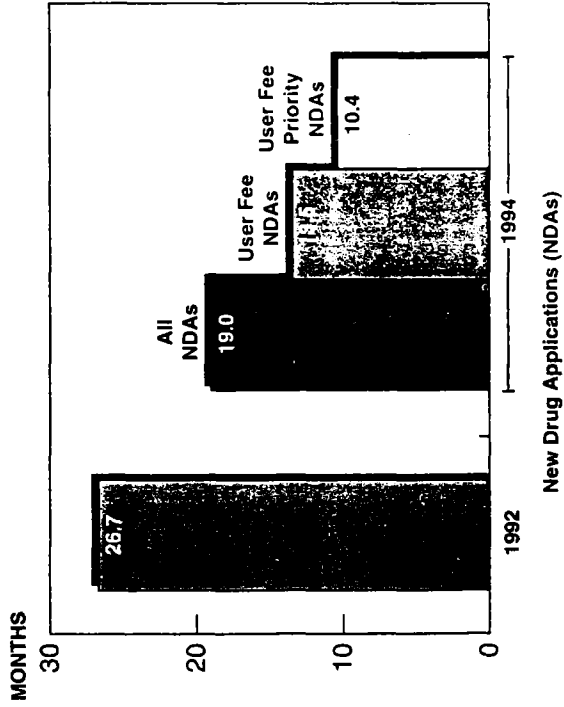
Clearly, we are in an era of change: the role of the patient in today's health care environment has changed; the pharmaceutical industry has experienced profound restructuring; new technologies and previously unknown illnesses must be understood; ever escalating health care costs challenge our ability to respond to ever increasing need. FDA has been working to meet the challenges these changes present.

Years ago, a case could have been made that the Food and Drug Administration was taking too long to approve drugs and that in

some cases, patients were disadvantaged by these delays. Whatever the truth of those allegations, they are not true today. Today drugs that offer significant improvement over existing therapies are approved as fast, and often faster, in the U.S. than in other countries with comparable standards. As a result of the Prescription Drug User Fee Act of 1992, we anticipate that drug review time will continue to improve further during the coming years.

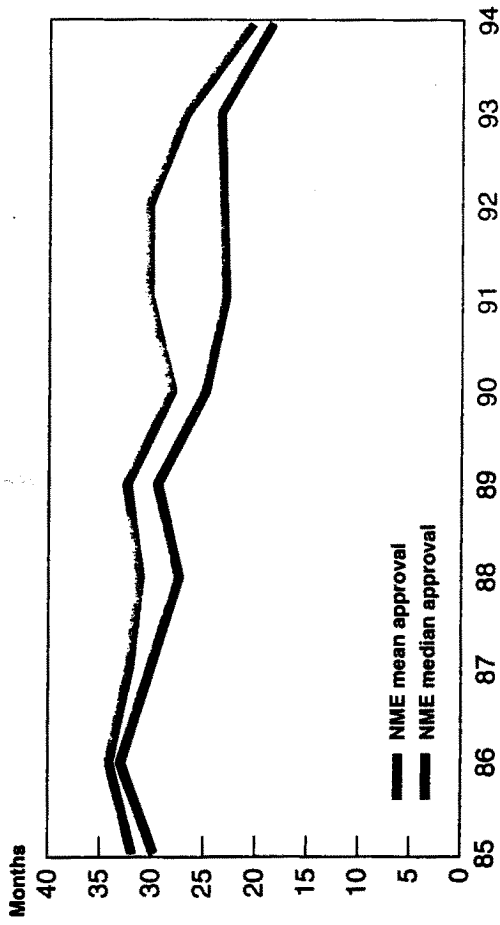
We have proven--and will continue to prove--our commitment to making FDA more efficient and responsive, while maintaining our high quality of work and the independence and scientific expertise that makes that work possible. In the end, it is FDA's independence that gives the American consumer confidence in the Agency's decisions. Our ability to meet our mission--to protect and promote the public health--should not be allowed to be compromised in the name of "reform".

Median Drug Approval Times



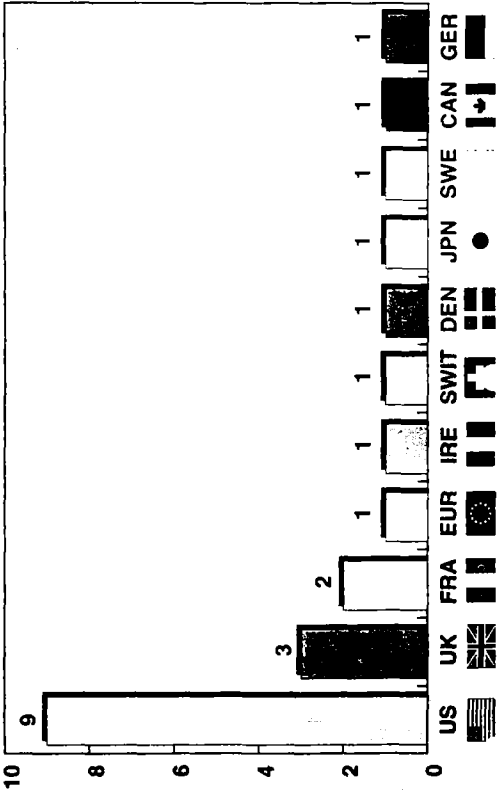
NME Time to Approval

Mean and Median



US NME Approvals in CY 94

Countries Where First Launched



n=22

Mr. McINTOSH. Thank you very much, Dr. Lumpkin. We appreciate your coming and testifying.

I have several questions, although I want to really address two, and then I will pass on to other members. If they do not get raised, I will come back at the end.

The first is related to something that came to us as we were putting together this particular hearing. Mr. Fox received a letter from one of the witnesses or people we had invited to become witnesses who had declined to come because, and I will read briefly from their letter:

"We have made the difficult decision as a result of our concern that our testimony may risk undue scrutiny and intimidation by the FDA and would cause severe stress, interruption of business and financial hardship to our small company."

Essentially we have been hearing from a lot of people that they are reluctant to talk about the agency because they fear retribution. When I held our first hearing of this subcommittee, I made it very clear that we would aggressively intervene in any case where we determined that somebody had been subject to retribution as a result of our efforts.

I wanted to not only ask you about that, but also ask if you would undertake a personal commitment to review that in the agency and, if cases come up, insure that appropriate action is taken to discipline the employees who may have overstepped the bounds in a way that does intimidate people from coming forward here in Congress.

There have been other examples. I think in the biologic area there was a newspaper report of somebody who has been calling up CEO's and saying do not bad mouth FDA. Remember, we are the one who approve your products.

I wanted to open that question generally, but also to get your personal assurances that you will do everything to prevent that from happening.

Dr. LUMPKIN. I think you bring up an absolutely critical point. Let me say at the very beginning that when I talk about having a process in which all Americans can be confident, part of that process is that it is an open, fair process.

The kind of things you are talking about—any kind of retribution or threats of retribution—clearly would not be consistent with an open, fair process. Let me make it clear that we will not tolerate that kind of behavior.

Now, I think we have to look at the realities of some of the types of allegations that are being made. I would like to say that we hear them also, and we are very concerned about them. I can assure you that if we have specifics on that kind of conduct, we will prosecute it to the absolute limits that we are able to do that because we do not want that kind of system.

I thought it was interesting at the oversight hearing with Mr. Bardin about 2½ weeks ago when that question was put to the CEO of Amgen, I believe. When he answered he said that he had not been personally involved. He knew of no personal knowledge of that going on, but he, too, had heard the rumors.

I think I am in the same kind of position he is in. I, too, have heard the rumors, but I have not had people bring forward to me

specifics of individuals or cases where this has happened. I would be very interested in it. I know Dr. Kessler would be very interested in it. I know our ombudsman, the IGA and all kinds of people who would be very interested in it. If any of the members here know of such things, please let me know.

Mr. MCINTOSH. I think you may need to take some positive, aggressive steps such as indicating if someone has complained against the agency there will be an assurance they will not be put on the reference list or some other means that they view as being very punitive.

Dr. LUMPKIN. Yes, sir.

Mr. MCINTOSH. Let me turn to one other substantive question, and this was the one raised by our witness, Ms. Gladis. Really I took two questions from her testimony and would like to pose them to you.

One was specific, and that was what are the chances that they are actually going to be able to get a treatment IND and a new drug approval for the drug Rilutek?

The other one is more general. She put it this way. What are we being protected from when she is likely to die of her disease fairly imminently? If there is a drug out there that may extend her life, even at some risk to her, would it not be better to let her make that choice?

If you could address both that specific and the general question?

Dr. LUMPKIN. Sure. Let me address the general question first, and then I will be happy to come back to the specific.

I think you bring up and she brought up the exact point I was talking about with so-called mechanisms we have in place. I think, just as you would imagine, too, that if any of us had the diseases that these people were talking about up here, you think about what would you want if you had the disease or if someone whom you loved had the disease. You would clearly want them to have access to anything that had the potential of helping them get through this. I think that is a very clear point.

People have to realize that when you are talking about making a benefit risk assessment that when you are talking about life threatening illnesses, there is a completely different risk benefit assessment than you have for illnesses for which there are less toxic therapies or more efficacious therapies available.

I think that from that perspective, that was the whole idea behind our treatment IND program. That would allow someone when the clinical data were being developed and you are beginning to get the early data that something is effective, but you know there is going to be the independent confirmatory data that is necessary plus the timing of assembling data and getting it reviewed.

You want people during that period of time to have access to something that they think might be beneficial. That is the whole idea behind a treatment IND program. I think there are ways that that lead can be met. Clearly there might be other ways. We are very interested in hearing if other people have that idea.

Now, as far as the idea of people making their own decision, I think that is exactly what the treatment IND allows. It allows the person before something goes on the market to make their own decision of whether, based on the data that they know about at that

point in time, to enroll in a program that allows them access to the drug while it is still not approved for general use here in this country.

As to the specific that you brought up of that particular drug, as the representative from the sponsor has already said, they admitted here in the open that they have put in a treatment IND. Under our regulations, the agency has 30 days to review the treatment IND and get back to the company. If the agency does not say there are any objections to it, it automatically goes into effect on day 31.

Beyond talking about the specifics because of the trade secret laws that I am bound under that Congress passed in the FD&C Act, I cannot tell you any more specifics about that review at this point in time, but I would be happy to give the committee and the Chair of the committee any information they would want on that in a nonpublic situation.

Mr. MCINTOSH. And so that 30-day clock has not lapsed in this case?

Dr. LUMPKIN. Not to my knowledge.

Mr. MCINTOSH. Good. Well, hopefully there will be good news coming on that question.

Dr. LUMPKIN. Yes.

Mr. MCINTOSH. Let me just put it another way, though. You have the treatment IND that requires the company to go through a fairly extensive process to apply for that and the possibility that it would be denied.

What would be the problem with changing the law to say look, if a physician wants to give a treatment to somebody who is suffering from a terminal disease that they will be able to give any type of treatment, as long as it does not cause their condition to worsen or shorten their life?

Dr. LUMPKIN. Actually, there is a provision in our present regulations that basically allows that to happen under the single patient IND. The treatment IND is kind of a generalized IND that would allow this to be done over a large population in the country.

Physicians can get their own individual IND, and it is not a particularly paper intensive process. I think it is one that we could make less intensive, but it is one that many physicians in this country avail themselves of in order to get unapproved drugs for their patients and to use them on an individual patient basis.

Mr. MCINTOSH. Are the companies allowed to notify them of the potential drugs?

Dr. LUMPKIN. I think there is within the scientific literature plenty of information. I mean, that is what people use to get the information out to physicians about drugs that are under development. You see it in all of the medical journals that come out during the months and during the development.

Mr. MCINTOSH. Which leads me to a whole other area of questioning, but I will defer that to some of the other members.

Mr. Peterson needs to catch his plane. I will call on him.

Mr. PETERSON. Thank you, Mr. Chairman. I will not take a lot of time.

You had two other charts in your testimony, Doctor, that you did not get to. I think I understand the second to the last one, but this last chart you have in there that has these graphs—

Dr. LUMPKIN. Yes, sir.

Mr. PETERSON [continuing]. You did not explain. Could you explain to me what that is?

Dr. LUMPKIN. I would be happy to.

[Chart.]

Dr. LUMPKIN. This was a chart that I was going to use if indeed the question came up, and it did, about comparing the United States' approvals to approvals in other parts of the world.

Again, this is a point I was trying to make relative to what happens if you look back at the decade between the mid 1970's and the mid 1980's and you look at the half decade between 1990 and 1994.

What this particular chart says is that if you look back at calendar year 1994, there were in this country 22 what we call new molecular entities. There were over 60 new drugs that were approved. Sixty-two it was. Of those 62, 22 were actually brand new molecular entities, meaning that that chemical had not been approved previously in this country in any kind or form.

When you look at those 22, in decades in the past often times you would say well, a great majority of those had been approved in other countries before they were approved here. We found very, very few back in the 1970's—it usually was around 15 or 20 percent—that were approved first in the United States.

Of those 22, nine were approved in the United States first. We were the first country for that number. When you look at the others, and you can just see the various countries there, the other drugs were approved first in those particular countries. That is all I was trying to show with that. We are seeing a change in this country of first approval.

It is interesting also, since the example of Great Britain was brought up, if you look back in the mid 1970's at the numbers of first approvals in the United States and first approvals in the United Kingdom, you will find that of that total number, about 75 percent were approved first in the United Kingdom.

If you look over the last 5 years, you will see that that splits about 50/50. That involves about 115 or 120 drug products. Half of those were approved first in the United States, and half were approved first in the United Kingdom.

Mr. PETERSON. One further thing. Could you explain to me then when I was over in Israel why we had American companies telling me that they had set up their operation over there because they could not get done what they needed to get done in the United States so they had moved the whole operation to Israel? There were quite a few of them.

Dr. LUMPKIN. I am not sure, sir, about many of the specific cases that you talk about.

It is interesting, though, that you bring up the question of Israel because there is a joint technology consortium that has recently been put together between the United States and Israel. We at the FDA have been invited to be a part of that and actually have been.

We have made several presentations to Israeli delegates and Israeli industry representatives about the drug approval process here in the United States and about the use of Israeli data and Israeli manufacturing processes for drugs to be marketed here in the United States.

ed States. There is a communicative process that is well underway there.

Mr. PETERSON. I think that there is that situation going on, but, as I understood it, the reason they were doing this is because they could not get done what they needed here and that they did not really want to ban it in the United States. This was some kind of interim step. I do not know. Maybe they just have not seen this new data.

Dr. LUMPKIN. That could be.

Mr. PETERSON. I apologize. I am going to have to leave to catch my plane. I appreciated being with you.

Mr. MCINTOSH. I thank you very much, Mr. Peterson. I appreciate you coming.

Let me ask one followup question on this chart. How many drugs not shown there were approved in those other countries, but not approved in the United States?

Dr. LUMPKIN. I can get you the data for the other countries. I have the data available for the United Kingdom, if that would be helpful to you here today. The data I have is 1990 to 1994.

If we take that 4-year period, in that period of time there were 104 drugs that were approved either in the United States, in Great Britain or both. Fifty-eight of those drugs during that period of time have been approved in both countries.

There are 28 drugs that have been approved in Britain that have not yet been approved in this country, and there are 18 drugs that have been approved in this country that have not been approved in Great Britain.

[Chart.]

Dr. LUMPKIN. Let me show you a little bit about those drugs. If you look at the drugs, there are 28 drugs that were available in the United Kingdom that are not available in the United States.

We went back and said well, what is the status of these drugs as far as the American market is concerned? There are eight of these drugs that have pending NDA's at the FDA, but all of those NDA's have been classified as standard, meaning that there are already approved alternatives to that drug in the United States to meet that particular disease need.

There is one NDA that has already been approved. It was approved in 1995 after this data was put together. There are two that, interestingly, the NDA's were withdrawn by the company while they were under review here in the United States because of safety problems that developed after their approval in Great Britain. Interestingly, both of those drugs were rated priority drugs for the American population, but because of the safety data in Great Britain, they withdrew them in this country.

There are eight that we have not received a marketing application for, i.e., an NDA, but they are under IND in this country, and there are nine of those drugs that we have neither an IND to study them in this country nor a marketing application for them in this country.

[Chart.]

Dr. LUMPKIN. If you also look at the next chart on the drugs that we have during that period of time that the British do not have, I think it is kind of an interesting group because of these 18 drugs,

many of these drugs were considered priority drugs for the American population.

Now, I cannot say whether or not these would be priority drugs in the British population because I do not know in the British pharmacopeia as to what they have or might not have already available.

If you look at some of these drugs, we are talking about drugs like Felbamate for unresponsive epilepsy; Gallium Nitrate for cancer related increased calcium levels; Histrelin for post puberty; Imiglucerase for Gaucher's disease; Stavudine for the HIV infection; Tacrine for Alzheimer's disease; and Succimer for lead intoxication in children.

I think you will all agree that these are very, very important drugs that are available in the United States during this period of time that are not yet available in the United Kingdom.

Again, you have to look at the data from both sides as far as what we have available here that they do not have and what we do not have available that they do have at the present time.

Mr. MCINTOSH. Thank you. I just wanted to ask you, what does NME—

Dr. LUMPKIN. I am sorry. New molecular entity, meaning it is a brand new chemical never previously marketed here. I am sorry for that.

Mr. MCINTOSH. Mr. Clinger, do you have any questions?

Mr. CLINGER. No questions, Mr. Chairman.

Mr. MCINTOSH. Mr. Fox, do you have any questions?

Mr. FOX. You have heard the testimony of the witnesses dealing with the companies that are trying to produce the drugs. You have heard the poignant testimony, I might add, from those who are waiting for the drugs, some of who receive, some who have not.

I think the bottom line is while the U.S. citizens appreciate the fact that the FDA is trying to make sure we have pure drugs and we know we are doing a good job of that as an agency and individuals, I think you also have heard very clearly and in a bipartisan fashion the fact that the country is reaching out saying we need to have help with these drugs.

As the chairman said a moment ago, people have illnesses where they may not have long to live and their life expectancy is at best questionable how long it will be. We need the agency to before we start regulating in areas that you think might not be advisable, is there a blueprint for speeding up the process so we do not export jobs, we do not export drugs and become the last country to have the benefit of the scientific and expertise from a medical point of view that we have educated here and could have been produced here, but has gone overseas because we over regulated ourselves out of existence?

Is there a blueprint from the agency that we should be aware of before we delve into new regulation that you will not like?

Dr. LUMPKIN. I am not sure we will not like the new regulation. I think we would be the first to say that I think there are a lot of things that presently exist that we would agree need to be dealt with. Perhaps some of the—

Mr. FOX. What would they be in simple terms?

Dr. LUMPKIN. In simple terms, I think some of the things that have already been pointed out as far as the issue of exports, as far as the old regulations on antibiotics and insulin, a lot of things that the RICOH initiatives have already begun to deal with. Most of these are going to take statutory reform in order to free us from some of the shackles that the FD&C Act has on us in those particular areas.

I think, though, getting really to the heart of the problem that you bring out, I think all of us who have looked at this problem realize that this is not a simple blueprint plan. There are a lot of different elements that play into this.

Clearly there is the issue of resources and having the people available, but I think the Congress and the industry—we have already taken that step. We have the user fee program that is well underway. Thus far, it has been very successful in meeting our needs and I think the needs of the country and the needs of the industry on that particular issue.

There is the issue, as the members of the pharmaceutical industry were talking about here, of looking at the overall timing of the development. You talk about this 12-year period of time. As was pointed out earlier, there is a part of that—the synthesis of the drug initially, the preclinical animal testing—that FDA has no regulation over per se. It is not under any kind you may start—you have to stop oversight of the FDA.

People have talked about dealing with getting in to people when you believe you have the data that you need. I think there are many of us that agree with what the people from the industry have been saying and who have been working with industry to try to highlight what are those areas within our regulations as far as formatting, as far as the data that need to be looked at that would allow them to get in to people more quickly in what we call phase I.

Mr. FOX. Let me ask you a question. What about the foreign testing? Can you take that? I mean, right now we are hearing from company after company and patient after patient that the foreign testing that is done by qualified companies in countries that have good standards like the United Kingdom. Can we without regulation make that change in your procedures?

Dr. LUMPKIN. I am not sure if I understand. Are you asking if we accept foreign data?

Mr. FOX. Yes.

Dr. LUMPKIN. Yes, sir, we do.

Mr. FOX. In all cases?

Dr. LUMPKIN. What is in our regulations, and I think it is a very good approach to foreign data, is a standard approach that I think most countries take as far as foreign data is concerned. We are willing to take foreign data as primary data of efficacy, provided there are several caveats on that data.

No. 1, the data have to be done under what is called the Declaration of Helsinki, which has to deal with the protection of human subjects. This is not for most companies a big issue. Most of the companies clearly are very ethical. They are doing the trials that way, and that is not a particular problem.

The populations that are being studied have to be applicable to the American population because obviously at the end of the day those are the people whom you have given us the responsibility for approving drugs for. In most cases, as was pointed out, the populations where these drugs are studied are indeed applicable to the American population.

There is the issue sometimes on antibiotic drugs because it is not the populations that are different, but it is the microorganisms that are different.

I think what you find in most of the larger clinical trials programs, as Dr. Blois was pointing out here earlier, is that the large, multinational corporations are doing global development. We will often end up getting pivotal studies both from the United States and from Europe.

That is basically the standard. We do accept the trials that are done in Europe that meet the caveats in our regulations as primary efficacy data. That already exists.

Mr. FOX. I am still troubled by the fact that I think there are probably AIDS patients and other patients waiting for drugs that they would have lived longer had they had the chance to have some of the drugs that are being held up by the procedures you are following that could be unfettered if you worked at it.

Dr. LUMPKIN. Again, I would like to know some of the specifics about which of—

Mr. FOX. The testimony we heard earlier from some of the witnesses made it pretty clear that some of the FDA's own over regulations or duplications of their own trials and the length of time or the number of trials required had caused delays in miracle drugs.

Do you need to have a waiver signed by patients or companies in order to move forward? Would that help you? Is it lawsuits that are concerning you?

Dr. LUMPKIN. No, sir. The concern that we see on particularly the life threatening diseases, as I think we have already discussed some previously, is that there are two needs that are having to be met. One is the individual patient's need to have access to a drug that he or she believes is going to be helpful to them.

There is also the community need to be able to find out whether indeed that drug does what it says it is going to do and can do it in a way that there is more benefit to the patient than harm.

I think what we have tried to do is weigh the balance of both of those through our accelerated approval, through our using the surrogate endpoints that accelerated approval has. We get AIDS drugs on the market in this country as quick as any other country for getting the drugs there. It has been interesting. The—

Mr. FOX. I do not mean to cut you off, but I think we need to accelerate the accelerated program.

Dr. LUMPKIN. OK.

Mr. FOX. I will be real clear about it. That is what they are trying to say today, these people who have taken the time and effort to be here. I appreciate that you are doing the same.

I think we really need to accelerate it geometrically. The fact is, for the people who are dying or who could live a little longer, I think we have to figure out a way. The community need comes sec-

and when it is their use of the drug that is a miracle drug that might help them. I think we need to find a way to get through that.

Dr. LUMPKIN. Sure.

Mr. FOX. I am finished, Mr. Chairman. Thank you.

Mr. MCINTOSH. Thank you very much, Mr. Fox.

Chairman Clinger.

Mr. CLINGER. Thank you very much, Dr. Lumpkin, for your testimony.

There is a lot of talk in Washington obviously about downsizing, streamlining, eliminating, combining and what have you. FDA is not immune from that exercise, both, I gather, internally and within the administration and within the Congress.

One of the suggestions would combine the Center for Biologics Research and Evaluation with the Center for Drug Evaluation and Research on the theory that they really have sort of parallel responsibilities and maybe we could do the same job as well in one shop. How does that strike you?

Dr. LUMPKIN. I have never worked in the Center for Biologics, so I cannot give you kind of a personal perspective on their procedures and what they do.

I think when you look at biologics there are, however, some very different kind of products that are there. They are the traditional biologics like vaccines and blood products, and then there are the new biotech products that are called therapeutic biologics.

I know the people have talked about that group of biological products having more similarities to the traditional chemical drugs, so that might be something that people would want to think about, as opposed to bringing both Centers together—to think about looking at just those products that might be more akin to the chemical drugs.

Mr. CLINGER. How badly stressed out is the agency now in terms of resources? We have heard discussion here that you are really having trouble keeping all the balls in the air and getting the work done.

Dr. LUMPKIN. There is plenty of work to be done. There is no doubt about it. I think one of the biggest things that our employees will come and say is a staff will come in and say what is our priority. It is kind of like in many other places I have been, whether it is Government or industry or academia.

They are all your priorities, whether it is doing new drugs, whether it is looking at new IND's, whether it is meeting with companies, whether it is answering congressional inquiries, whether it is dealing with the press. There is a whole gamut because people in this country are interested in drugs. It affects every American in their medicine cabinet. That is part of the reality of working there.

I will say that as far as the new drug review process is concerned, the user fee program has been a godsend. There is no doubt about it, not only from a human resource perspective, but an infrastructure resource.

When I came to the FDA in 1989, when I went to my division this was a division responsible for all of the antibiotics in the United States. It had 66 staff members and not one fax machine. In

fact, they had a policy that they would not take faxes from companies.

When I went there they had kind of an nascent e-mail system. There were two desktop computers in the entire division. That has been changed because of the user fee program because we have had the dollars not only to invest in human resources, but to invest in infrastructure that will bring this agency into the 20th century as we begin to go to the 21st century. That has been a remarkable improvement in resources.

Mr. CLINGER. One of the suggestions is all the user fees are not actually going directly to speed drug approvals. Is there a siphoning off of some of the user fee resources for purposes other than direct approval of the drug approval?

Dr. LUMPKIN. I can speak only to the Center for Drugs. I will tell you that at the Center for Drugs, we are fully aware of the statutory language that says these dollars must be spent for what is defined in the user fee statute as a review of human drug products. That is what we have spent the dollars for.

As with any other kind of that kind of program, there are obviously the internal and the congressional Government audits. We are ready for that. I do not think there will be any problem if somebody audits the spending of the dollars that the Center for Drugs has done.

One of the things I think is interesting that was part of the program that people may not realize is that the dollars were clearly additive dollars onto the base appropriation level that existed in 1992.

Because it is a 5-year program that is scaling up the employment on the human resources side over a 5-year period, we knew that in the first half of the program the majority of the money that we had coming in was going to be available to spend on infrastructure because the human resources were going to be a much smaller portion of the expenses at that point of the program.

As we now are building up to the FTE, full-time equivalent, ceilings that are allowed under the program, clearly a much, much higher percentage of the dollars are going for the human resources salaries part of it.

I think you will see as we do the congressional financial reports in the coming years that the percentages are going to be switching from infrastructure to human resources simply because of the increase in numbers. That is the way the program was outlined.

Mr. CLINGER. Finally, the suggestion was made by a number of the industry panelists and others that the agency should make greater use of outside resources for the clearance process. Do you want to comment on that?

Dr. LUMPKIN. Yes, sir, I am happy to. I think there are several issues that we need to think about when you think about using outside resources. First of all, we actually do use some outside resources at this point in time.

One of the elements of the user fee program or the user fee legislation is that we are prohibited from using user fees to pay for those, but that is again an issue that can be dealt with.

We have had both success in failures in using outside reviewers. I can tell you about some of those because I think it gives you some

of the problems and some of the good sides that people have to think about on this.

One of the real problems that we have even with reviewers that are in-house is the issue of consistency in the sense that you want to make sure and we want to make sure as upper management there that if Company A comes in with a marketing application to use their drug to treat a certain disease and Company B comes in with a marketing application for their drug to treat the same disease that there is as much as possible consistency in what the standards are for those drugs because they are going to have to compete in the same marketplace, and there needs to be consistent standards on the inside.

One of the concerns that we have had and that we have seen in some of our outside resources in the past is that when they are spread throughout the country and are not part of the overall development of the various policies and are not there during the review process, we tend to get even wider swings in consistency than we get with in-house representatives.

Other questions that have been brought up have to do with the fact that when we have dealt with outside reviewers, the reviewers that we have had the opportunity of dealing with have not been able to review full-time. They have jobs on the outside that they are also doing, whether they are academicians, whether they are working at various other jobs. We only have them for a partial period during the day, as opposed to a resource that we would have in-house on a much more full-time basis.

One of the issues prior to the user fee problem—the user fee program; it is hardly a problem—was that not having the resources available, we had to look on the outside. What the user fee program I think has done is provided us with in-house resources to do our job.

One of the things that people have been talking about here that I would like to put back to the panel is that from a management perspective the beauty of the user fee program is it gave us goals. It said these are your performance goals that you are going to be held to. The process for getting there is up to you. That is your management job. We are not going to micromanage you, but we are going to hold you to these performance goals.

I think that is a very legitimate management tool to use performance goals as a method of saying this is your responsibility. If you cannot do it, then your process is broken, and we need to go back and look at the process. If we are able to use our process to meet those goals, then I think from a management perspective we have done what has been asked of us.

Mr. McINTOSH. Thank you, Mr. Clinger.

We are running somewhat short on time, but I want to make sure Mr. Tate has a chance to ask questions.

You have to catch a train at 2 p.m.? Is that right?

Dr. LUMPKIN. Yes, sir.

Mr. TATE. Then we will be leaving together.

Dr. LUMPKIN. Pardon?

Mr. TATE. We will be leaving at the same time.

Dr. LUMPKIN. OK. That is fine.

Mr. TATE. We are catching the same train.

Dr. LUMPKIN. All right.

Mr. TATE. I, too, would like to thank you, Dr. Lumpkin for coming by.

You may have mentioned this, and maybe I did not catch it in your testimony. What are you folks doing in regards to reduction of paperwork in regards to new drug applications?

Dr. LUMPKIN. I think the biggest thing that we have in reducing paperwork is the use of our electronic submissions. People have talked about in the past these 100,000 page documents that come in. Indeed, we do have 100,000 page documents that come in, and they are a tremendous problem to us if for no other reason than finding a storage place to put them.

I think what we have been working with, and industry has been absolutely wonderful in working with us on this, is trying to come up with electronic ways of submitting. Most of our larger applications now are submitted in an electronic format.

It clearly helps us on the review process of being able to use electronically formatted NDA's to go through the review and evaluation process. That is one of the biggest things that we have at this point in time.

Mr. TATE. What would you say would be the average number of pages for a new drug application like 3TC, for example?

Dr. LUMPKIN. For what? I am sorry.

Mr. TATE. For example, like 3TC. How many pages would they have to fill out?

Dr. LUMPKIN. It really varies, depending on what the disease entity is. Let me give you the extremes, for example.

Our experience has been if you are developing a new, general use antimicrobial and you know that in order to be a competitor in the antibiotic marketplace you have to have five, six or seven indications approved with your drug at the time that you go to market here not so much because the FDA requires it, which we do not, but because in order for you to be competitive with the buyers that are out there, you have to have a good product, those particular NDA's usually will run somewhere between 100,000, 150,000 or 200,000 pages when you talk about manufacturing procedures to preclinical to clinical data, all the data put together.

There are then other products that are called, for example, line extensions. If you have a dermatological product that is already approved as a cream and you want to now make it as a lotion, those things will often only have several hundred pages, if that many, in them. They will be clearly much, much smaller.

We do see a very large differentiation there, depending on what they are going for.

Mr. TATE. If they are filling out 150,000 pages, for example or 200,000 or 100,000 or whatever, are every one of those necessary? If so, for example, like on 3TC are there any that you suggest that are not necessary?

Dr. LUMPKIN. From what I have seen from my experience as a reviewer, the pages that we ask for for the most part are necessary.

I am sure there are things in there that we could think about doing without. Particularly, for example, one of the initiatives that has been put forth was the one dealing with the environmental assessment. I think, for example, we know those are very costly for

companies to do, and we know that when you look at our experience over the years that we have not had a problem that has been picked up by our review of the environmental impact in the production of drugs that come through our shop.

That is one of the things that we propose to do away with, but that is taken care of by other people. We do not need to do that, and the companies do not need to do that for us. There are, yes, sir, things that I think we could do away with in there.

Mr. TATE. If I can ask one quick last question? Have there been any studies by your particular agency on how much time it takes for these companies to fill out these forms?

Dr. LUMPKIN. Let me say this.

Mr. TATE. It seems to me to fill out 100,000 pages; I mean, just filling out our tax returns takes forever——

Dr. LUMPKIN. Right.

Mr. TATE [continuing]. Let alone filling out 100,000 pages.

Dr. LUMPKIN. They are not filling out forms that we end them, for example.

Mr. TATE. Right. I understand. They are doing the studies and so forth.

Dr. LUMPKIN. Right. Right. These are pages of reports that they send in.

I can only speak from my own personal experience. I know that when we were putting together applications for submission to the agency when I was in industry they would often take—obviously it is being done in a project managed way that as you finish one thing you are beginning to get that part of the application ready and it is all kind of going in a concurrent process there, but it clearly takes in many respects between 6 months to a year to finally get everything put together to send it in.

Mr. TATE. Is that taken into account in the requirements you have as to how long it takes? Is that any part in the factoring in of what you are requesting, how long it takes to fill these things out? Is that part of the equation?

Dr. LUMPKIN. I think it is. It clearly is part of——

Mr. TATE. The more you have to fill out, the longer it takes to get these drugs approved, which drives up the cost. It is costing lives.

Dr. LUMPKIN. I think the question that you are going to is not an issue of just what to fill out, but whether it is necessary——

Mr. TATE. Exactly, on both ends.

Dr. LUMPKIN [continuing]. To fill out the forms.

Mr. TATE. How long it takes, and also if you are filling out forms that take this long and you are discussing whether you should even get rid of them all together in regards to environmental concerns, it seems like a waste of time.

Dr. LUMPKIN. Right, and I think that that is exactly what people were going to, as I was saying, particularly——

Mr. TATE. Especially when people need these particular drugs and so forth. It seem to me that there is a lot that can be done to speed that process up to really save people's lives or make their lives better.

Dr. LUMPKIN. I think we agree with you.

Mr. TATE. I look forward to working with you.

Mr. MCINTOSH. Thank you, Dr. Lumpkin.

Let me say that I would like to keep the record open. There are several questions that I had that if we could, I will submit to you in writing. One of them will have to do with a subject that I guess I want to say a few statements more than a question.

You mentioned the use of medical journals as a way doctors can get information about the use of drugs. The whole issue of regulation of off label uses and distribution of information about that and regulation of information on cost effectiveness I think is an area where the agency, quite frankly, has made a stupid decision in terms of trying to regulate and manage that.

What they ought to do is focus their efforts on making sure that it is true information and not try to restrict the type of dissemination of information as long as it is true and accurate because one, you are not going to be able to do it. It is going to be like nailing jelly to the wall. It is going to go all over the place, and people are still going to get the information out. Two, I think it also does a disservice to the patients and the medical community when that effort is made.

Some of my questions have to do with that. I hope we can pursue a discussion of that area and that you will take that back to the agency because I know some of the other offices are also engaged in that type of effort.

Dr. LUMPKIN. We will be happy to answer that.

Mr. MCINTOSH. All right.

Dr. LUMPKIN. We would be happy to discuss it with you.

Mr. MCINTOSH. Thank you. Thank you for coming. I do appreciate it.

Dr. LUMPKIN. It is my pleasure. Thank you, sir.

Mr. MCINTOSH. Our next segment of the hearing is what we refer to as the open mic segment.

Let me introduce Karen Barnes, who is one of the staff members for the subcommittee. Karen will be making the mic available to people who would like to testify. I know several people have indicated to Mr. Fox and to Karen that they would like to testify during that time.

If I could ask you to state your name for the record and any written testimony you have provide to Karen so that we can put that into the record? Also, please keep your statements as brief as possible so that we can get as many people as we can in during this time; ideally 3 minutes. If you need a little bit longer, we can do that.

Karen, why do you not start out.

Mr. FISHER. Mr. Chairman, I am Dr. George Ross Fisher. I practice in Philadelphia, and I am a member of the House of Delegates of the American Medical Association, although I am not speaking for them.

I am submitting for the record a copy of my resolution to the AMA, which will be considered next week after their amendment deliberation.

My remarks may seem radical to you. I am addressing my remarks to the subject of whether the Kefauver amendment is entirely wise; that is to say whether the focus of the FDA on efficacy is wise.

Before the Kefauver amendment, the Food and Drug Administration was concerned with safety. I am sure that in Senators' and Congressmen's minds it was helping the country be rid of snake oil salesmen who could claim almost anything would "grow hair on a billiard ball and make childbearing easy."

Obviously it is a sensible thing, which I support, to forbid the sellers of drugs, whether they are drugstores or manufacturers, to make claims which cannot be supported. I am not advocating immediate repeal of the Kefauver amendment. I am advocating that we take another look at it.

Previous speakers today have addressed the matter that of course we want drugs of proven effectiveness. That makes a good line. That is a good point, as I would think of it, because the Food and Drug Administration, and let me quote you, "... recognizes that the FD&C Act does not limit the manner in which a physician may use an approved drug."

Once a product has been approved for marketing, a physician may choose to prescribe it for uses or treatment regimens for patient populations that are not included in the approved labeling.

I think if you examine the process by which the manufacturer achieves approval for an indication of efficacy, you can see that he is unwilling to spend millions of dollars and take years of time to receive approval for things of limited market value. Therefore, the efficacy requirements of the FDA are inherently limited.

The efficacy as stated by the FDA will never be a comprehensive list of what the drug is for. That could lead us to a situation in which physicians are afraid to prescribe a drug, even though they have a perfect right to prescribe it, because it is not one of the listed approvals.

They are fearful that they will find themselves in court facing a plaintiff's attorney who says well, you used this drug and the patient then died. You used the drug and it was not approved. Well, it was not illegal, yet it was not approved.

By twisting that around, you can see the chilling effect on the medical professional of having a book, Physicians Desk Reference, which I understand there are a million copies printed a year, half of them sold in book stores, which lists these approvals and indications with the implication that the medical profession is limited to them when they are not.

There are several of the Medicare carriers, one in Louisiana in particular, who have started to refuse to pay for certain drug regimens in their jurisdiction—it has not happened to me—because the drugs were being used for a purpose that was not an approved purpose.

Nobody ever claimed that these approved purposes were comprehensive, but when they start to limit your ability to have Medicare pay for them, you can see that the whole process here of the Kefauver amendment, which had a benign purpose when it started, is now a subject which I feel ought to be re-examined and relooked at.

Mr. McINTOSH. Dr. Fisher, if I could ask you to go ahead and summarize, that would be great.

Mr. FISHER. That is all I have to say. I would be glad to answer questions.

[The prepared statement of Dr. Fisher follows:]

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Improvements in the Regulation of Drugs
 Testimony, June 9, 1995

George Ross Fisher, MD
 Trustee (Philadelphia), Pennsylvania Medical Society

Mr. Chairman, let me thank you for the opportunity to comment on possible legislation for the improved regulation of the Food and Drug Administration.

To begin, let me submit a photocopy of a resolution to the American Medical Association of which I am an author. It will be considered by the House of Delegates of that organization on June 18, and is subject to their amendment and deliberation. My testimony today is therefore as an individual. For the purpose of today's testimony, attention is best directed to line 16 of page 2 of the discussion draft of Congressman Fox's bill. Reference is made there to investigations necessary to "assure the safety and efficacy of the drug being investigated."

When the Federal Food, Drug and Cosmetic Act was first enacted, and for decades thereafter, the quotation would not have read like that. Reference would only have been made to safety. During all that period of time, the evaluation of efficacy of prescription drugs was the responsibility of the physicians who prescribed them, and the federal government confined its regulation to assuring that the drug was safe for physicians to use. What they used it for, was a matter of professional determination.

The late Senator Estes Kefauver then sponsored the current additional responsibility of the FDA that it assure that a new drug has at least one proven medical use before it is released for prescription. Senator Kefauver might not have phrased it just like that, and I am uncertain what combination of regulation, statute and policy achieves that result, but this has been the effective result of the Kefauver Amendment on the practice of medicine. The FDA carefully stipulates that once the initial approval of a drug has taken place, physicians may then prescribe approved drugs for any unapproved purpose that seems useful in their professional judgement, as you can see in the appended photocopy of a page from the PDR (Physicians Desk Reference).

Pharmaceutical manufacturers would summarize the Kefauver Amendment quite differently. The manufacturers are strictly limited to advertising only the official uses which have passed the elaborate tests of efficacy specified by the FDA. On many occasions, I have asked drug representatives about uses not specified in the approved package insert. They prove extremely uncomfortable about such questions, and refuse to comment. Nevertheless, the medical literature

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abounds with articles describing success with unapproved or off-label uses, and I am quite free to use the drugs if I believe what I read.

This awkward situation leads to implausible consequences. Many drugs enjoy wide-spread use by the medical profession for purposes and indications which the manufacturers are not permitted to claim. This appears to come about when a drug has passed the efficacy test for some minor purpose and then develops a patent or competitive commercial situation which makes the manufacturers unwilling to spend the rather huge sums required to achieve FDA approval to advertise the extended indications. At the same time, many physicians are inhibited from employing the drug in useful ways because they can see in the Physicians Desk Reference there is no FDA stamp of approval for that use. They can easily envision themselves in a courtroom accused of doing unapproved things, and are often convinced plaintiff attorneys will characterize the situation as unorthodox if not improper. In other words, even if such use is not illegal, it is unapproved. You would not want your doctor to do unapproved things, now, would you?

We have reached a situation in which a drug requires twelve years and a hundred million dollars to prove even one point of efficacy. No further indications receive FDA sanction unless the manufacturer is willing to spend more years and millions to get the sanction. Indeed, manufacturers are often reluctant to produce a different sized tablet because of the cost to them of achieving FDA approval for a smaller pill. This is true even though I as a physician have a perfect right to prescribe a different dosage and have the local druggist make it up in a capsule. If the proposed use has only a small sales potential, or if the patent protection has only a short duration, the manufacturer will not pay for the clinical trials. The FDA is too overburdened with other applications to do it on its own initiative. And so, some physicians run an unwarranted malpractice risk by using the drug, while other physicians are too timid to stray beyond the published approvals; and so their patients are deprived of benefits. It would be far better if the FDA were completely silent about efficacy.

The efficacy requirement imposes an even worse problem at the beginning of the process. Until the manufacturer has established some sort of efficacy for some kind of problem, the drug is unobtainable. For years I have been hearing doctors with foreign accents praise the diabetic drug Metformin, and read many articles in the medical literature which convinced me of its great superiority. Finally, this January the FDA agreed with the rest of the world. Marketing of the drug was surprisingly delayed until May. For years I had been treating diabetics in ways I knew were inferior to Metformin, only to hear from the manufacturer's representative that patent had expired and the manufacturer was therefore dubious for a while about marketing the drug in the US at a profit. This Gilbert and Sullivan comedy only occurred last month, but already a dozen of my patients have reported gratifying results from a drug I knew was excellent 16 years ago.

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Now, for a solution I do not urge Congress to go so far as to repeal the Kefauver Amendment entirely. It is a good thing to be rid of unproven or even fraudulent claims. I do not want to hear it claimed that eating peach pits will "grow hair on a billiard ball and make child-bearing easy." What I desire is a legal sanction for the release of drugs for physician prescription when they have passed the appropriate FDA tests for safety. Statements about the efficacy of such drugs would be strictly limited to articles in peer-reviewed journals, available only to the medical profession. I would not object to some sort of licensing process for such peer-reviewed journals, thus providing a way to revoke the license if the journal strayed from scientific rigor. In summary, I propose a stage in drug development intermediate between the pre-Kefauver and the post-Kefauver situations. In this new stage B, a drug would be found to be sufficiently safe for use, but not yet approved for advertising of its efficacy. There might be room here for further refinement, but I urge Congress to leave that to the medical profession to work out. Should usage of a Stage B drug be limited to indications found in peer-reviewed journals? Possibly, but I am uncertain. There will be other sessions of Congress if you find you have created a loophole. It is also possible that you might create a Stage B, but for some reason drug manufacturers prove unwilling to release drugs into that limbo.

This sort of subsidiary question leads me to the thought that Congress needs to creat some sort of oversight or FDA evaluation commission to report yearly on the evolving complexities of drug evaluation, availability and advertising. Congressman Fox has proposed such a commiission, and I would urge the inclusion on it of representatives of the American Medical Association and the Association of Retail Druggists. Pharmaceutical manufacturing representatives are valuable, but they may feel constrained to blunt their criticism of an agency which can bankrupt them. Similarly, academic medical centers are so dependent on federal grants and the overhead allowances attached to them, that they, too, may fear to speak out with the opinions Congress would want to be aware of.

Mr. MCINTOSH. Thank you.

Any questions for Dr. Fisher?

Mr. FOX. If the six doctors that are coming up, Mr. Chairman, could remain for questions after the group has spoken, or do you need to leave right away?

Mr. FISHER. No.

Mr. MCINTOSH. Do you want to do it that way? OK. I would be glad to schedule it that way.

Mr. FOX. We will ask you questions after we finish the other doctors. Thank you, Doctor.

Mr. MCINTOSH. There were several other doctors who wanted to be included in this section.

Dr. Robert Sklaroff I think, was the next one.

Mr. SKLAROFF. You have my typewritten testimony. Mr. Chairman, thank you for the opportunity to discuss the impact of the FDA upon the daily experience of a practicing oncologist.

You have already heard from Dr. Fisher. He encourages the FDA to focus its work upon toxicity of drugs, products and devices rather than just on their utility.

I had opposed former President Reagan in terms of how some of his ideas may have had an impact on the first 100 days contract.

The key point here is to see how the Government can be streamlined in order to achieve freedom and in fairness. Government should guide the citizenry. It should neither dictate its activities nor engage in "laissez faire." At least in my opinion, removing the efficacy requirement would unleash the FDA, allowing it to protect without unduly restricting innovation.

I found it quite startling to listen to a defense, if not an apology for the 150,000 to 200,000 page application with justification that the applicant entity wants that length because otherwise the drug will not be marketable such as the antibiotic. I found that to be disingenuous.

Last week a colleague told me that the HMO created by Travelers Insurance Co. for Medicare patients had decided not to finance the use of Taxol against lung cancer. You heard about Taxotere here earlier today.

Taxol, or powdered Taxotere, is a first-line therapy for ovarian cancer, although you did not hear that mentioned with respect to ovarian cancer earlier today. This is based on that major knowledge that we have.

Lung cancer is the major cancer because of cigarette smoking.

Although this affords few therapeutic options, particularly in response to Taxol, thus is access to an active drug effectively banned.

Doctors are acutely aware of the limits of this, so we often test a series of agents until we find one which works for a given patient. Being patient advocates, we cannot ignore anything which would help in 1995, despite the absence of definitive data.

The advent of restricted formularies which are generated by insurers are regularly precluding the ability to entertain such alternatives. We would invite you to share receiving the gratitude of a patient who has achieved tumor regression, or alleviation of her ailment symptoms, from chemotherapy or any other treatment if she felt therapies were required which would enable legislation

perhaps through implementation of a faster fast track, as Representative Fox suggested earlier.

Deafness to progress has been justified by citing the absence of FDA approval as cited in the PDR. The use of a given agent in the appended resolution to the testimony I provided, and I cite the third Whereas, which Dr. Fisher cited earlier.

It is this firmly forced upon the pharmaceutical houses exorbitant sums to overcome. What I do not understand is the justification that new agents were not necessarily emulated in America. It may very well be because of the overall cost of submitting an IND. In the interim, under the guise of FDA determinism, indicates therapy is denied.

Certainly the FDA should disclaim responsibility for determining if a new drug is any better than a related drug. This is a hot topic with me because I was very interested in Vinticin, which is a sulphate. I studied it as a Fellow. Eli Lilly tried to get it approved, but it was not considered to be any better than the others. Therefore, it was not approved. A lot of us still feel it is the best one for lung and esophageal cancer, and we feel that these diet pills should have been allowed to compete in the open market.

Off-label prescriptions, which we have discussed here earlier, are routine. They are drawn from recent knowledge gained from reading foreign literature and reviewing presentations. I want to give you an example, which is close to my heart right now.

I have a patient who is my age with malignant melanoma metastasized to his brain, to his skin, to his liver. I read the ASCO abstracts, which is the American Society of Clinical Oncology, which suggest a certain drug may do him a favor. I gave it to him. This is off label.

I am waiting to see what happens and whether or not he will be covered on an outpatient level by the insurer. Although I thought it was a long shot, it was the best we could offer him right now. This is something that happens commonly, as discussed previously.

Regarding the issue of cost, everyone can explain why the other guy should pay for a given service. This is really the part I would like to explain to you that has not yet been discussed.

When clinical research requires financial support, patients look to insurers, insurers look to academicians, academicians look to industry, industry looks to Government and Government looks to patients. Cannot this loop be broken?

How might the FDA promulgate policies which could facilitate and compensate 85 percent of the patients that arise in community hospital settings, not just for cancer?

This is why the NCI established the CCOP program a decade ago. That is the Community Clinical Oncology Program. Here the local hospital physician sort of flip flops. Instead of the usual situation when the academic center contracts to a local entity to conduct clinical research, in a CCOP the local entity was funded and then it choose which academic institutions with which to relate and where to acquire their clinical protocols.

It was anticipated the composition of the study group would reflect the entire population having a given malignancy in the community because of the fact they would be using a community based effort.

Last week, Pennsylvania State Representative, Elinor Taylor, appeared with reference to the court-mandated coverage of dose intensive chemo with autologous marrow transplant or peripheral stem transplants as a treatment for metastatic breast cancer.

I figured rather than make myself responding to that, I would look at the whole issue and suggest that they be merged, the clinic with academics and research, along the line that that described.

I called for the creation of a seamless system designed to integrate care, and I noted that some streamlined process would probably stimulate the composition of user friendly standardized studies. Large scale studies listing cardiology also, but there is really no methodologic approach that would cover, for example, neurologicals, as you heard earlier discussed.

Mr. MCINTOSH. If I could ask you, Dr. Sklaroff, to go ahead and summarize your testimony?

Mr. SKLAROFF. That was the part of it. I suggest that this structure would have insurance coverage for the basic medical care and additional coverage through either the academic institution or through the pharmaceutical house promoting the drug to cover the other aspects of it.

I close basically with the fact relating to tobacco and also relating to the recent information that came out from the FDA a couple days ago. The coverage of tobacco, because it is a toxic issue, should be maintained by the FDA. Similarly, when the FDA requests reports on problems with blood vaccines, again this is a toxicity issue which I feel belongs underneath the FDA, and these two current samples do not undermine my major feeling that the FDA has indeed denied this push.

Therefore, I am suggesting a national system for clinical research benefiting the patients without jeopardizing their safety. I explain why and a cost-effective level in the last paragraph.

Thank you.

[The prepared statement of Dr. Sklaroff follows:]

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June 9, 1995

to: U.S. Rep. Jon David Fox

re: "Improvements in the Regulation of Drugs" - Draft Testimony

Mr. Chairman, thank you for the opportunity to discuss the impact of the Food and Drug Administration upon the daily experiences of an oncologist. I will follow-up Dr. Fisher's comments regarding the Kefauver Amendment and add other points regarding how your efforts could provide focus to the FDA's activities. The key concept which will be explored is how to integrate research into the clinical setting, ensuring reimbursement for delivery of basic medical care.

Government should guide the citizenry; it should neither dictate its activities nor engage in Laissez Faire. Thus, removing the "efficacy" requirement would unleash the FDA to protect Americans without unduly restricting innovation, and the insertion of an intermediary "stage" in the approval process would create a structure which would encourage use of new drugs earlier than now occurs.

Last week, a colleague told me that the H.M.O. created by Traveler's Insurance Company for Medicare patients had determined that it would not finance the provision of Taxol to patients with lung cancer. This disease affords limited therapeutic options, and many researchers consider Taxol to be a first-line agent; therefore, they're upset that it cannot be offered to their patients.

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In the past, such decisions have been justified by citing the absence of FDA approval for the use of a given agent for a particular indication. It is this hurdle that costs the pharmaceutical houses such exorbitant sums to overcome. In the interim, patients are denied access to agents that can help them.

Physicians prescribe drugs "off-label" routinely, drawing upon knowledge gained from reading foreign literature and/or data recently presented at meetings. For example, earlier this week, I prescribed ultra-high dosages of tamoxifen for the treatment of widely-metastatic malignant melanoma, a type of aggressive skin cancer. This decision was based upon information which had been presented only a fortnight earlier during the annual meeting of the major world-wide cancer organization, the American Society of Clinical Oncology. This decision was also based upon my knowledge of the drug and its mechanism of action from prior readings, thus undermining any claim that oncologists would merely engage in "cookbook medicine." We're patient advocates, and we're reluctant to deny a patient any treatment which could work in 1995, even if definitive data may not be available until 1996 (or beyond). Life is too short!

Yet, as "restricted formularies" are generated by insurers, such alternatives will be precluded regularly. Certainly, the FDA should disclaim responsibility for determining if a new drug is "any better" than a related drug which has already been marketed; this type of thinking blocked release of an anti-cancer drug called Vindesine--desacetyl vinblastine amide sulfate--a decade ago, despite the claim by some oncologists that it had greater efficacy than other members of the family of "vinca alkaloids" (made from the periwinkle plant) when treating lung and esophageal cancer. If the drug works, it should be released, allowing it to "compete" freely in the open market with other agents.

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Oncologists are aware of the limited utility of our armamentarium, and we are often eager to try a series of agents until we might find one which "works" for a given patient. The FDA's restrictions often serve to preclude this approach. Our patients would be grateful were you to remove obvious impediments to the availability of new drugs; such legislation would cost the government nothing.

Regarding the issue of "cost," everyone can explain why "the other guy" should pay for a given service. When clinical research requires financial support, patients look to insurers. Insurers look to academicians, academicians look to industry, industry looks to government, and government looks to patients. Cannot this loop be broken?

How to harness the force of patient responsibility will not be addressed here; using Medical Savings Accounts is cited as a key proposal dealing with it. What, then, is the parameter which determines whether patients become involved in clinical research? And--whatever this consideration may be--how might government establish policies which would facilitate the conduction of quality clinical trials? And--whatever the protocol might be--how may community-based patients acquire such agents, without having to travel to university settings?

For cancer, the Clinical Cooperative Oncology Program (CCOP) was established; the local physician/hospital contracts with an academic center through which its clinical observations are added to those drawn from a large patient sample. In this way, it's anticipated that the entire population having a given disease will be reflected in the composition of the study group. Large-scale studies exist, also, for cardiology patients, but there now exists no methodical approach to implementing such a system for patients with other diseases.

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Last week, I responded to PA State Representative Elinor Taylor's request for data regarding the use of "dose intensive chemotherapy with autologous bone marrow transplantation or peripheral stem cell transplanation as a treatment for metastatic breast cancer." Rather than limiting myself to providing her a summary of the major studies being conducted in this field, I emphasized the need to merge academics and research with the clinic. I noted that the newest cancer protocols are not routinely accessible to the 85% of patients treated in the community setting. Finally, I called for the creation of seamless systems designed to integrate care, and I noted that this structure would probably stimulate the composition of more "user-friendly" protocols for each cancer patient. This would force a standardization process to occur, streamlining the study of each tumor-type.

The structure you may wish to consider adopting is to identify prospectively those facets of medical care which are basic--regardless of the type of therapy --and those which would be necessary because of the specific characteristics of the agent(s) or approach(es) to be employed. The former would be insurance-covered and the latter would be divided between the research entity and the pharmaceutical/industrial entity promoting the proposed innovation. Those who would be composing the overall program would be able to base decision-making on relevant practice parameters generated by professional organizations. Thus, the "self-interest" of the advocate for the utility of a given treatment would be subsumed by acts of those who would ensure that "the protocol should be fit into the patient, rather than the patient fit into the protocol."

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The FDA would be involved in the above proposed processes, to the degree determined by how enabling legislation might control its oversight functions. Illustrative of the national implications of FDA approval--as cited in the Physicians' Desk Reference--is the appended AMA resolution; it cites a rejected claim by HCFA (in the third "Whereas" paragraph) ascribed to a PDR reference.

These same approaches could be applied to the tobacco product, inasmuch as the cigarette serves as a nicotine-delivery device. Regardless of whether it is felt to be "addictive," this drug shouldn't be exempted from FDA-oversight.

This isn't a tangential consideration, for smoking remains "Public Health Enemy Number One," and the FDA shouldn't shirk its power to fight the pandemic of diseases caused by cigarettes. . .which, indeed, the above scenario would not preclude. This scourge on the world society--as well as our own--wouldn't receive "FDA approval" were it introduced today, and the necessity to acquire a prescription for its acquisition would surely curtail a lot of its use.

To summarize, I endorse both the insertion of a new stage in drug-development, and the development of a Congressional Committee for FDA Oversight, as detailed by Dr. Fisher. Further, I suggest consideration be given to creation of a national system for clinical research, whereby the cost incurred when providing basic medical care could not be ignored by insurers, and whereby the cost incurred when providing a new therapy could not be ignored by academicians and by private industry. The former idea would prove cost-effective, for it would ensure the FDA would work to facilitate development of new drugs; enacting the latter idea would cost the government nothing. And both would benefit patients without jeopardizing their safety. Thank you for the opportunity to speak with you this morning. If there are any questions, please do not hesitate to ask.

Mr. MCINTOSH. Thank you very much.

Let me ask you, Doctor. Are you able to see David holding up the time remaining?

Mr. SKLAROFF. I did not. I was looking around. I did not see him.

Mr. MCINTOSH. David, apparently the witnesses cannot see you keeping the time. Can you do it in a way that they can do that?

Our next witness is Michael Sperling. Are you able to see David, Dr. Sperling?

Mr. SPERLING. Yes, I can. Thank you.

Mr. MCINTOSH. You might stand somewhere where they can recognize you.

Mr. SPERLING. I will be very brief. My name is Michael Sperling. I am a neurologist specializing in the treatment of epilepsy. I have extensive experience in treating patients with professionally approved drugs and also with investigational drug trial tests. That is testimony that I will not reiterate for the panel.

I have a couple of general comments after listening to all of the statements made this morning, and that is that I think we would all agree, those of us working in the field, that new drugs are expensive and come to the market very slowly or do not come at all. It would be most helpful if the cost could be brought down and the efficiency improved.

I think the paperwork issue is an important one that needs to be addressed and that specific goals be given to the FDA for reducing paperwork and time. Each patient has a booklet about this thick, two or three inches, that we have to fill out for each individual person undergoing a trial for 3 months. That just snowballs. It is not surprising to hear of hundreds of thousands of pages being developed.

My overall conclusions would be to advise that the FDA be given incentives to approve drugs, that they need to issue some sort of annual reports regarding the number of completions, how many completions and how many rejections.

One other comment I think I have to make now which I was not planning on making, but from past testimony I will make it, is in regards to the efficacy and safety issue. I think it is going to be absolutely key for efficacy to be maintained. That is why the FDA mandates it. Otherwise patients will suffer in the long term.

If I as a doctor and other people as doctors knew that a patient could choose whatever we want, no matter how ineffective it may be without any evidence, over the long run many people will suffer.

There is a form of leukemia now that has a 1 in 90 percent cure rate. If we could give whatever we thought over the last 20 years without insisting upon these kinds of trials, we would still probably have a 90-percent fatality rate.

To jump in and say I know what is best for you and I want to take a long shot is reasonable under certain circumstances, but there needs to be efficacy or else society in the long run will suffer, which means individuals like you and I will suffer over the long run.

[The prepared statement of Dr. Sperling follows:]

Statement of Michael R. Sperling, M.D.

My name is Michael R. Sperling, and I am Chief of the Medical/Surgical Program of the Comprehensive Epilepsy Center at Graduate Hospital in Philadelphia and Associate Professor of Neurology at the University of Pennsylvania. I appreciate this opportunity to talk to you about the needs of the approximately 1.6 million people in the United States with epilepsy.

My neurology practice is largely devoted to treating people with epilepsy. Medications that are currently approved by the FDA control the seizures of only 60-70% of patients. Therefore, they are inadequate for 500-600,000 people, for whom epilepsy remains a serious problem. People with epilepsy have a high incidence of associated mortality - the death rate averages one in 200-300 per year. They are also prone to such problems as injuries, burns, fractures, cognitive problems, and such social impairments as the inability to drive, with resulting social isolation and limited occupational opportunities. Many are unemployed or underemployed. The direct and indirect costs to the health care system and society are therefore enormous. Better drugs are needed to treat this condition.

I have treated thousands of patients with epilepsy who are inadequately controlled by the currently approved medications. They continue to experience seizures, often with devastating effects on themselves and their families. Family life is strained as people try to cope with the illness, and sometimes a family member must devote much of his or her life to caring for a relative with epilepsy. Some people resort to sending overseas for medicine approved in other countries when approved medications in the U.S. fail, but most simply suffer with their symptoms and wait for new medications to reach the U.S. market.

Medications that are currently approved for treating epilepsy have many side effects that also make the development of new agents desirable. The drugs can produce symptoms that diminish the quality of life, and none are ideal for pregnant women. The common drugs for epilepsy also change the way our bodies metabolize other medicines, and therefore complicate the treatment of other medical conditions.

Much has been learned about the physiological causes of epilepsy in recent years. We are now in an unprecedented position to take advantage of basic research to design new drugs. These could be more effective in treating epilepsy and have fewer side effects than the medications now available. Their development should not be forestalled because of inappropriate and inordinately expensive testing. Moreover, many of the new drugs might work on one specific mechanism to prevent seizures and thus be useful for only a small subset of patients. The cost of development might not justify the expenditure needed to bring it to market.

No new drugs were approved to treat epilepsy between 1979 and 1993. While three new drugs were approved in 1993-1995, only two are currently in use, and they have limited applicability. More than 20 compounds are currently being tested, and many more could be developed. However, the regulatory system discourages development of new agents with limited market potential due to enormous startup costs.

Let me mention some of the current problems preventing the development of new epilepsy drugs and suggest some solutions.

Problems

New drugs take too long to reach the U.S. market, and some never make it. Lamotrigine

was available in Europe for many years before FDA approval, and vigabatrin has been used in Europe for years and has yet to arrive. Other drugs, for various reasons, may never be available here.

The paperwork required for clinical trials is enormous, adding costs and thereby discouraging the development of new drugs.

Sometimes, the FDA approves a drug for such a specific use that it discourages wider use of potentially beneficial drugs for others with the same condition. Some of the medicines approved for "adjunctive" therapy could be given alone, for example.

Inappropriate cautions are sometimes added to labeling by the FDA for no logical reason. This discourages appropriate use of the drug. FDA approval is sometimes delayed for an inordinate time after FDA advisory panels have recommended approval.

Pharmaceutical companies are often discouraged from testing new medications in many of the people who might need a new drug, such as children or the elderly, because it makes regulatory approval more difficult and complicated. Consequently, wider use is discouraged after a new drug is approved.

Suggestions

There must be an incentive for FDA personnel to approve drugs. Now, all the incentives favor delay.

The FDA should issue annual reports regarding the number of completed evaluations, including approvals and disapprovals, and should specify how much time the process took.

The natural course of illness must be considered in the regulatory process. A two-year delay from submission of documents to approval is excessive, particularly when that might mean thousands of unnecessary deaths. The FDA should have a defined time period in which to accept or reject a new drug.

The amount of paperwork must be reduced, but reforms should not allow ineffective or inappropriately risky drugs to reach the market.

Some testing protocols should be allowed to measure new drugs against conventional therapy, rather than requiring some patients to take no therapy at all.

Mr. MCINTOSH. I cannot resist, because there is a disagreement between you and Dr. Fisher on that.

Would you, as a doctor, ever choose a drug that medical journals were saying was 90-percent effective? Would you choose something that was less effective?

Mr. SPERLING. No, I think not. I think the issue is—there are two issues here. One is that these things are sometimes not approved by the FDA. Because the literature does show that it is advantageous, therefore we will use it, even though the FDA has not approved it.

I am talking about drugs where there is really very little data or no data at all to support it. A single trial or a single report where several people got something and it seemed to be effective really is not active scientific proof. I think the proof in the pudding is that the vast majority of IND's prove the policy of preliminary data usually does not pan out, or it suggests a rigorous scientific study.

Mr. MCINTOSH. Your concern then is not that people will ignore the data, but that there will not be a sufficient incentive for the companies to prove that their product works. Simply because of marketplace you need the regulation in addition?

Mr. SPERLING. Precisely, and I think that is a very important point that needs to be made.

Mr. MCINTOSH. Thank you, Dr. Sperling. I appreciate it.

Our next witness we would ask to participate in this is Dr. Jack Cionci.

Dr. Cionci, thank you for joining us.

Mr. CIONCI. First of all, I would like to apologize for being a little bit late this morning. My testimony is now at the door, so when you leave you can pick up a copy.

I would like to thank Congressman Jon Fox for inviting me here, and I would like to thank the distinguished panel and also everyone that is in this room that is concerned about this issue that really impacts public health for everyone.

I have been in general practice since 1950, and I never had a single malpractice case brought against me. I have to owe a lot of that to the FDA because the drugs that I prescribed, the FDA made sure that they were safe and efficacious, thereby removing many pitfalls of litigation. I consider the FDA one of my guardian angels. This was in 1950 when I first went into practice.

Decades later, along comes AIDS. It is an entirely new ball game. It is in a new arena, and we need new rules. The FDA must move with the times. We must put aside our politics and put aside our prejudices. We must open up our hearts to our brothers and sisters who are HIV positive.

The paper that I wrote was written with a great deal of help from members of Philadelphia FIGHT, of which I am proud to be a member. The people who are HIV positive helped to write this paper. It is an expression of their views of what they would like to see done as far as new regulations from the administration.

We need the fast track, and we positively need the FDA to guarantee uniform dosage strength and quality assurance. We need documentation of side effects and efficacy.

Many members of the HIV community join buyer clubs. These are mostly underground where you go into Canada or into Mexico or overseas. The problem is people have tried this, and some of them have died.

I can give you an example of Compound Q, of which at least six people independently taking this drug died. It may have been due to inaccuracy in the strength they were taking because there was no one looking over their shoulder to guarantee the dosage that they were taking. This is where the FDA comes in and does a remarkably good job.

Up until now, AIDS has been nearly 100-percent terminal. I am saying nearly because we have long-term, nonprogressives, people who have had this disease for years, beyond the 10 years that they are usually told they have when they are first diagnosed.

You have heard the eloquent testimony of my friend and colleague, Kiyoshi Kuromiya, who publishes the Critical Path, which I consider the premier medical monthly AIDS newsletter. I say medical because I use this as a reference every month when it comes to my doorstep. I pray that Kuromiya continues to be a long-term, nonprogressive.

In closing, I would say just as we physicians who treat people with HIV ask the nations to join in the management of their care, so should the FDA grant these same people decisionmaking on which drugs they may like to test.

These patients, my friends, have everything to gain and nothing to lose. It is their body and their life.

Thank you.

[The prepared statement of Dr. Cionci follows:]

Congressional Testimony on FDA Regulation
Jack Cionci, MD

I thank you very much for the opportunity to testify before this committee. My name is Dr. Jack Cionci. In 1988 I made a decision to devote my semi-retirement to helping people with AIDS. I have been involved in many projects both here and abroad since that time. One of these projects is the Community Advisory Board of Philadelphia FIGHT, our local community research Initiative that sponsors clinical research in AIDS in the primary care setting.

People living with HIV in the Philadelphia metropolitan area are very concerned with the issue of FDA regulation because many believe they are being denied access to potentially life saving therapies because of the arrogance and paternalism of that agency. In most other areas involving medicine, the trend over the past thirty years has been away from paternalism, and toward the belief that adults are entitled to make their own decisions about their own medical care. Only in the area of new drug development does this trend move in the opposite direction. Only in the area of new drug development do we have an agency that feels entitled to refuse to allow people facing a life-threatening illness to make their own decisions about treatments.

The clearest example of the heartlessness and arrogance of the FDA that we have seen in Philadelphia has come over the Salk Vaccine. Jonas Salk, one of the most distinguished scientists of the twentieth century, developed an approach that he felt might prevent people from getting sick, even if they had the AIDS virus. In tests in California in the late 1980's the vaccine was shown to be safe. In wider tests in several cities it was again shown to be safe, and there is some data that indicates it works. There are local physicians, and researchers in several academic centers, in addition to Jonas Salk, who believe this drug might have some efficacy, and that it should be more widely tested. Yet for over two years now, the FDA has refused to allow this drug into wider trials. We are particularly aware of this issue in Philadelphia because many of the trials for Salk vaccine were conducted here. In 1992, over 1,000 people signed petitions circulated by ACT UP asking for access to this drug. Many of those people are

now sick, or dead. They have died waiting for this vaccine to be tested. No one has asked the FDA to release the drug to the market without further tests. All that has been requested is we test the drug to see if it works. Yet the FDA continues to refuse.

The Salk Vaccine illustrates the real problem with the FDA system when it has to deal with a life threatening illness. Whether the drug is safe is not in question. There is a significant amount of data indicating that it is safe. The issue is efficacy, whether the drug works. That is what we are trying to see tested. The FDA is not yet satisfied, they claim, with the preliminary efficacy data. Yet why should this prevent the drug from being released for testing? Salk Vaccine won't hurt anyone, and it might help.

The efficacy issue comes from a fundamental confusion, we believe, in the minds of the bureaucrats who control the FDA. Much of this regulation is believed to stem from the Thalidomide incident in the 1960's, where a drug that did cause major birth defects was kept off the American market by one FDA official who prevented a potential tragedy. But Thalidomide was a sleeping pill. Thalidomide at that time was not considered a drug with efficacy against a life threatening illness. There is a difference between Thalidomide and drugs, such as Salk Vaccine. The difference is the difference between a sleeping pill and a potential treatment for a disease that will almost certainly kill you if left untreated. Any system that is unable to distinguish between these two categories should not be making its own rules.

Another way of putting this problem involves which risk we should take more seriously. The FDA seems to be fearful of making the mistake of allowing a drug to market that does not work. The opposite risk, of withholding from the market a drug that does work, does not seem as important to them. But for people living with HIV, that risk is desperately important.

Finally, the FDA's refusal to accept any foreign data further contributes to this problem. The result is that drugs that are approved all over the world, including European countries are denied to people in the United States while pharmaceutical companies jump through bureaucratic hoops, and people with AIDS

have to smuggle drugs into this country -- assuming they have the means to pay cash for them -- in an attempt to save their lives.

The cost to the pharmaceutical companies to jump through these hoops is enormous. As a result, only the biggest companies can afford to stay the course. Smaller companies either must seek a larger partner, or, in many cases, give up. Another story we are familiar with in Philadelphia illustrates this point. The drug involved was called Imreg, and it was, like the Salk Vaccine, an immune modulator. It looked promising in early tests. The company thought it was working well with the FDA. Then, unexpectedly at an FDA hearing, new questions which they company had not been aware of, were raised by the FDA. Eventually it led to accusations that the researchers in the study had known who was receiving drug and who was receiving placebo. Eventually, the company, unable to raise continued capital was forced to give up. Two years later, a scientific review of the data involved in Imreg was published. The reviewers found no basis for the accusations made against the researchers in the study. This review was published in the peer reviewed scientific literature. But by then it was too late. Let me emphasize this point: the physicians who conducted this study in Philadelphia, which included two leading researchers at a major AIDS hospital, were convinced that the data showed promise -- and that their patients were doing better and staying healthier. Was it the cure? Probably not. But it could have been a drug that helped people, and it was destroyed by the Food and Drug Administration and their arrogant bureaucrats.

As we have looked into this as activists, we have come to believe that one of the reasons this problem occurs is the system of peer review that the FDA employs. Supposedly neutral outside scientists are brought in periodically, and asked to comment on proposed drug trials. There are several problems with this system. First, as far as we understand it, while the outside reviewers are supposed to state direct conflicts of interest (although this seems to be only a recent development) they are not required to disclose conflicts involving research on products that might compete with the drug under study. In other words, if their research funding will directly benefit from the failure of a competing drug, they are not required to disclose this. Second and more important, the main goal of a reviewer attending these meetings is career

related. In other words, the goal is to be asked back. This creates pressure to conforming to the party line of the FDA, and the party line of the FDA is not necessarily in the best interest of people with AIDS. There have been published descriptions in books about AIDS, including the recent "Good Intentions," and "Acceptable Risk" of what has gone on at the meetings of review panels. These discussions, which I urge you to read or have your staff read, include comments from individuals on the review panels for AZT and other drugs in which they describe a party line literally developing over lunch and a decision inexplicably changing.

Of course it is easy to criticize. I would not want to limit my statement to criticism without addressing at least briefly how it could be a better system. The system for approving drugs for life threatening illnesses should be as follows: small safety trials, followed by a limited release of the drug with a requirement that the company continue to collect data. If a company fails to continue research, the drug could be withdrawn from the market. Currently the FDA puts huge artificial roadblocks in the way of drugs being released, and then turns around and does NOT require companies to continue to collect data. The most well known example of this in the AIDS arena is DDI, where it is generally believed by clinicians that we will never know the best way to use this drug because it was released based on limited data (a position I would support) but then the company was never held to its commitment to continue to collect data. John James, the editor of AIDS Treatment News, a very well respected treatment newsletter, has made a number of proposals along the lines that we would support for how to move drugs through the system more quickly. I hope the committee will take the time to familiarize yourselves with some of these proposals.

Finally, regardless of the specific remedy, we believe the power of the FDA needs to be reduced, and they need to understand that there are a government organization that is paid by the people of the United States to work for them. They seem to believe that their scientific expertise somehow gives them the right to make moral and ethical decisions for the rest of us. The decision where to draw the line on safety vs. efficacy is not really a technical issue. It is a matter of public policy which citizens and their elected

representatives should debate. Scientists should provide the necessary background information, but policy makers and the public should make the policy. Then technicians can decide how to apply the policy.

Currently the bureaucrats at the FDA seem to feel they have the right to tell people faced with life threatening illness how much risk they should be allowed to take. More than that, they seem to feel they have the right to tell people with life threatening illness that they can't use a medicine until they, the FDA, are sure it works. But, if someone plausibly thinks it MIGHT work, then if I were a person living with this devastating disease I would say: let me and my doctor be the judge of that, not some faceless bureaucrat.

Thus on behalf of people living with HIV in the Philadelphia area, let me say that I hope Congress will act to curb some of the power of this agency. We need regulation. We do not need arrogance and insensitivity to the needs of people with life threatening illnesses.

Thank you very much for this opportunity to appear before you.

Mr. MCINTOSH. Thank you very much, Dr. Cionci. I think that is a very eloquent statement of the problem in some ways.

Our next witness is Dr. Jungkind. Welcome.

Mr. JUNGKIND. Thank you. I will be brief because I realize how late it is. I will just tell one very brief story with four very brief components.

One of the areas that I did not hear touched on at all, and it may have been touched on earlier, is that the FDA regulates diagnostic devices, lab tests. This is an area that I think is a relatively new area of their regulation. It is an area that they are just getting their stride in. Unfortunately, their stride is going down the same wrong road that they have taken with over regulating some of the drugs.

The very brief thing that I need to say next is that I have been working on development of laboratory tests for over 20 years. We have done over 3,500,000 tests. I have had hundreds of employees over the years and have helped bring many, lab tests to market and have been the primary test site for several FDA approved audits.

I have seen the FDA gradually change over the years to the point where something that was a very good scientific study published in the best journals and the amount of paperwork involved with that, evolved to my last clinical trial where I walked into the office and my whole office was filled with boxes of paper. I thought maybe they had accidentally shipped me the entire paperwork for the entire Nation! It was just for a few hundred patients, and this was a result of the new FDA rules coming into diagnostic devices.

The next component of the story I want to say is how would you like to be the person that just won the Nobel prize for creating one of the greatest scientific discoveries in microbiology technology? This is an American, Dr. Cary Mullis, who discovered the polymerase chain reaction. Right after that, a number of other people discovered some very similar kinds of techniques.

The technique has the ability to alter a major segment of our clinical laboratory testing detecting for infectious diseases. It is possible to detect a unique fingerprint of every infectious organism and do it very rapidly and effectively and give a rapid, accurate diagnosis. What good are the drugs if you really do not know what is the infecting agent? If you can speed diagnosis up, it will help the patient recover.

How would you like to have the FDA with their new set of rules making it so that we are the last country on earth to get to benefit from this technology, the last industrialized nation?

Europe is well ahead of us. I just completed the major clinical work on a major piece of automated equipment. Where is it going to be introduced first? It is going to be introduced in Europe. Japan has it. Europe has tests for HIV, tuberculosis, hepatitis C plus the one that finally was approved in the United States, chlamydia, which is the most common sexually transmitted disease in industrialized nations.

It to me just seems laughable that here is the technology that is American as red, white and blue. Everyone else in the world is getting to use it and not us because the companies are afraid of the FDA; in fact, so afraid that one of the FDA people that has

changed sides has published a book on how to deal with the FDA that is a little over \$500. If I could just review for you a little bit of the advertisement, I would close.

The book tells how we have gotten to dotting the i's and crossing the t's. It is not whether it really works and is good. It is not scientific. It is just looking for irregularities. Even a tiny irregularity can result in delays, fines, black listing.

The fear of the FDA that results in this kind of book makes it so the small companies do not bring out the diagnostic devices as quickly as I saw in earlier years, and it takes the large companies years before they finally bring products out. Even when they do, they use them everywhere else. We are the last place that they are willing to tackle.

If you could change that and make it so that we just had to prove equivalence, which is the way we used to do it, it would be better. Instead we must try to prove that it is better. If it proves equivalence we could then allow the scientific community to gradually through evolution make it better just the way the airplane got better as the years went on.

Thank you very much.

[The prepared statement of Dr. Jungkind follows:]

Comments

Donald Jungkind, Ph.D., MT(ASCP)
Diplomate, American Board of Medical Microbiology.
Professor of Microbiology and Pathology
Director of Clinical Microbiology.

I have had extensive experience working with diagnostic devices used to perform laboratory tests during my 22 years directing a clinical microbiology laboratory in a major medical school hospital. My laboratory has done approximately 3.5 million laboratory tests in that time. I have also been active in research, development, and clinical trials of diagnostic devices (often called test kits). I have worked with numerous major manufacturers of these devices. Much of this work has been presented at national meetings, published, and submitted to the FDA. My list of published presentations and scientific articles has approximately 85 entries, including two books. In short, I know a lot about lab tests, how they work, and how they get to market. As you know, this is one of the major areas that the FDA regulates. This area is also one that has recently received increased regulation from the FDA.

Have these new efforts on the part of the FDA been constructive or destructive? They certainly have fostered more attention to detail, but is it the right detail, or is it wasted effort? History as usual is the best judge. I have seen most of the relevant history, and have seen lab testing develop from manual methods in the three main lab areas, chemistry, hematology, and microbiology, to a highly automated system in chemistry and hematology. Unfortunately, the science to automate microbiology was not discovered until recently. Noteworthy is the fact that the high degree of sophistication and automation in chemistry and hematology occurred during a period when the FDA had a more appropriate approach with regard to

1 diagnostic devices. During those years from the 1960's until the late 1980's, the field of
2 clinical laboratory science made tremendous advances in areas where automation was
3 possible. The academic and health care industry brought to market equipment, test kits, and
4 techniques that have brought down the cost of chemistry and hematology testing dramatically.
5 If we think health care is expensive now, try doing the same number of tests nationwide, but
6 with a manual system. You would see costs increase several fold. Moreover, there were great
7 improvements in the accuracy and the types of tests that were generally available to the public.
8 These golden years of development occurred without the degree of FDA regulation that is in
9 place today. If increased regulation had been in place then, I feel that progress would not
10 have happened as quickly. We can be grateful that major advances in reducing the cost-per-
11 test through automation have already occurred in two of the three major laboratory areas.

12 Now, there is technology that makes it possible to begin to automate the last major
13 area of lab testing - the clinical microbiology lab which helps with diagnosis of infectious
14 diseases. In my opinion, the development of this new technology is being slowed by the
15 increased FDA regulation in this area. Never before has it been more important to keep up
16 the rapid pace of new lab test development and automation. It is common to read about new
17 infectious diseases, new strains of old diseases, and antibiotic resistant microbes that are
18 evolving. These demand rapid responses in our ability to test and evaluate these infections.
19 Moreover, efforts to lower costs in clinical microbiology laboratories, one of the most
20 expensive sections of the lab because of the manual nature of the work, is being hampered by
21 the slow development of automation and slow acceptance by the FDA of the new molecular
22 based technologies. Why is it that the country that made the major advances in molecular

1 biology is the nation reaping the least medical test benefit from this technology among
2 industrialized nations? For example Dr. Cary Mullis, an American discovered the first of the
3 DNA amplification technologies - the polymerase chain reaction (PCR). He won the Nobel
4 prize for his discovery. His discovery makes it possible to diagnose many diseases, especially
5 infectious diseases faster and better than ever before. It can be a new gold standard for
6 detection of microbes. Moreover, PCR and related amplified DNA based technologies such
7 as LCR, SDA, BCA, and NASBA can be automated, eventually resulting in reduced labor
8 costs that can lower testing costs in microbiology as it has for chemistry and hematology.
9 We can also give better care which eventually lowers costs as well. An example is more
10 accurate and faster diagnosis of tuberculosis which can save thousands of dollars per case.
11 However, development of these new technologies is being slowed because of the over
12 zealous rules and requirements that the FDA has imposed on test development. The FDA
13 requires proof of equivalence to existing technologies for most new lab tests. However, the
14 FDA requires a much higher standard for these new DNA amplification based tests.
15 Specifically the FDA has imposed more complex clinical trials for these tests. I am actively
16 involved in these and other clinical trials. The new FDA regulations have raised my research
17 costs dramatically. It costs me roughly double to do clinical trials now. Moreover, I don't
18 think that the trials are any better when measured by production of a better product. There is
19 more detailed record keeping, more extensive case history recording, and more attention to
20 "the FDA game" rather than focusing on the science. To illustrate the general awareness of
21 the increased number of problems that the new FDA regulations can cause, there is a newly
22 released book costing over \$ 500 to help us understand and play the new "FDA game".

1 During the period of rapid development in chemistry and hematology in previous
2 decades, the FDA approved devices and tests based upon equivalence. One aspect of *in vitro*
3 diagnostic testing that sets it apart from other health care disciplines is that clinical
4 laboratories are expected to rigorously evaluate each new laboratory test (without any
5 possible patient ill-effects) versus their current test system before implementing the use of the
6 product into their laboratory test regimen. The results of these studies and evaluations, many
7 of which are published in peer reviewed scientific journals or presented at scientific meetings,
8 ultimately determine the success of new diagnostic products. In effect, these studies
9 performed by individual laboratories surpass in importance the studies performed by the
10 product's manufacturer for FDA approval. FDA approved products can evolve by a process
11 of new discovery, improvement, and competition at a more rapid developmental pace due to
12 the creativity shown by the many doctors and scientists making the evaluations that follow
13 after FDA approval. Many of these evolutionary changes could never have been predicted and
14 incorporated into original FDA studies. Now, the new FDA regulations hold our country
15 back by changing the focus from equivalence and subsequent evolutionary improvements, to
16 simply trying to guess what the FDA wants and trying to meet their checklist and
17 expectations, which can be arbitrary and can change.

18 While most of the DNA amplification technologies were discovered and developed
19 here in the USA, Europe and Japan have more DNA amplification tests than the USA. We
20 have only one approved test. The rest of the world is already benefiting from better tests for
21 TB, AIDS, and hepatitis C. They will be benefiting from the lower costs of automated test
22 systems at a time when in the USA, we will not even have started our clinical trials. The

1 USA, which used to be first, with the Coulter counter in hematology, the automated Beckman
2 glucose analyzer, and the automated Technicon chemistry analyzer, is now the last, because of
3 the increased FDA regulation. I know that the FDA means well, but development and
4 acceptance of new technology is a scientific and medical decision. Better to let the scientific
5 and medical community have a greater role in the decision to accept or reject a new
6 technology. Scientific publications in peer reviewed journals by clinical laboratory scientists
7 reporting the performance of new products and technologies are more useful to the clinical
8 laboratory community than the current, more extensive FDA review process.

9 Also, the FDA should accept test devices that have been accepted by other
10 industrialized nations without requiring extensive retesting here. My experience recently in
11 doing clinical trial research has been one of making sure that the "I" is dotted and the "t" is
12 crossed, with no real scientific benefit. I have seen companies be much more cautious with
13 marketing and development of new tests in this country. It is not because they don't have
14 good ideas to develop, but they have to dedicate more of their financial and human resources
15 to get new tests through the FDA. Moreover, smaller companies may not be able to compete
16 at all. Remember that many of our breakthrough ideas belong to small companies.

17 I think that the FDA's efforts to help, will actually hurt more people because there will
18 be less rapid improvement and advancement than there could have been. I could give
19 numerous examples to illustrate these points, but there is not time. I think it is time for the
20 FDA to return to a more appropriate level of regulation and allow the scientific and medical
21 community a greater role in determining which tests to use, and how to use them to greatest
22 advantage.

Mr. MCINTOSH. Thank you very much, Doctor. Actually, it is fascinating. I think we have had three views on the question of efficacy and very helpful insight.

I, unfortunately, must depart at this point, but I am going to turn over the gavel to the vice chairman, Mr. Fox. There were some questions he had for the doctors who participated, and if there are any other people, Mr. Fox, if you could let them also contribute their testimony.

Mr. FOX. Absolutely.

Mr. MCINTOSH. I appreciate it. Let me repeat that it is an honor for the subcommittee to be here, and everybody from Montgomery County should be particularly proud of Jon. He is doing a great job on our subcommittee and the hearings we have had in Washington. It is an honor to have him as our vice chairman.

Thank you very much, and thank you, Jon, for completing this.

Mr. FOX. I just wanted to thank Mr. McIntosh before he leaves.
[The prepared statement of Dr. Ginsberg follows:]

June 5, 1995

PAPER ON THE SUGGESTIONS FOR MODIFICATION OF THE PROCESS FOR DRUG APPROVAL IN THE UNITED STATES

Comments on Monitoring And Review Of New Drug Applications And The Clinical Process Through Which Drugs Become Approved

These comments are based on my experience dealing with the FDA for thirteen years and my involvement in approximately 300 pharmaceutical studies during that period of time. In almost every instance the FDA has moved appropriately and has made reasonable decisions as to the efficacy and safety of the drugs in question. It is important to note that the FDA must walk a very fine line in the drug approval process because if it moves too rapidly to approve a new medication it exposes a population to a risk involving unknown side effects. Also if someone is using a new medication that is not efficacious, it keeps that patient from being given an opportunity to use other therapeutic modalities which may have some effectiveness. On the other hand, if the FDA moves too slowly, it may prevent efficacious modalities from being applied to a population. This, of course, has come to the forefront most noticeably in the treatment of AIDS. Again, it is important to understand that frequently public expectations are heightened by the press and they do not understand all of the ramifications and potential dangers of new medications. It is said that it takes a million doses of a medication to develop a side effect profile completely so

that almost any drug can, at some point in time, demonstrate new side effects and dangers. Therefore, understanding these considerations, the job that we ask the FDA to perform is almost an impossible task in that it is incredibly difficult to predict how chemical moieties are going to effect a complicated biological entity such as a human being and on the other hand delays in approving effective medicine may certainly cause people to suffer or die.

It is with the previous comments in mind and with the application of my thirteen year history in doing drug development that I would, however, like to make certain suggestions as to techniques that I believe will make the drug approval process more expeditious.

I would like firstly to suggest that we must do everything as a society to encourage the development of new and innovative pharmacological weapons in our on-going battles with disease. To this end, I would suggest, that for any product which is considered the first of a new class of drugs, the company which worked to develop it be given an extension of the exclusive period in which they have to market it. I would like to see the developing company given an increased opportunity to recoup its developmental cost. So, for example, if it's normal to give a seventeen year patent on a new chemical modality, I would like to suggest that it be extended to twenty-one years in cases of unique or innovative drugs. This, of course, does not keep other drugs of the same class from being developed, but it will encourage the chance that unique or innovative drugs be preferentially explored.

Another suggestion that I would like to voice at this point is that we increase the degree of standardization in all aspects of the review process. There is too much reliance on the individual bias of the reviewers, so that, frequently a pharmaceutical company is pointed in one direction and then there is a change in a reviewer which requires redirection. This adds expense and time to the approval process. I would like, therefore, to suggest that there be standard clinical pathways for a variety of therapeutic areas so that a company going into the approval process will have an excellent idea of exactly what type of studies are required in the developmental process. I would like to see specific pivotal studies required for areas such as hypertension, adult on-set diabetes, congestive heart failure, etc. There is no questions that each drug has different potentials and different dangers, and of course, these individual variances will have to be addressed, but the better that everyone understands what is required going into the process, the quicker the approval can be accomplished.

I also would like to suggest that the same standardization process be applied to the monitoring at the investigational sites. It has been my personal experience that the monitoring is very much dependent upon the individual biases of the Reviewer at the clinical sites. Frequently, as an investigator, one feels that they are uncertain as to what exactly the FDA is looking for in its field trips. Also, as a related issue, most of the monitors coming out to the sites have limited medical knowledge. They come to visit my site on one day, and the next day, they visit a water ice manufacturer to determine the purity of their process. I believe that it is vital and imperative that we have medically

knowledgeable people monitoring the clinical sites. Also, I think it is better to monitor the clinical trials as the trials are in progress as opposed to several years after they end. This would expedite the process. To this end, I would suggest that the FDA involve knowledgeable medical people on a local level. That is, to organize a national network of medical personnel, preferably physicians, who would be willing to monitor and review studies as they are in the process of happening as opposed to retrospectively. This would allow ongoing dialog with both the pharmaceutical company sponsoring the study and the FDA as to any potential problems in the carrying out of the study and as to their independent appraisal of the drug in question.

Also it is vital to expand standardization onto an international level. Clearly, we are becoming a global community, particularly on a medical or pharmacological basis, and medical problems which crop up in Africa, Europe, or other parts of the world eventually bear directly on the population here. The drug approval process has to be considered in a world-wide context. I understand that this is being done currently, but I believe that great efforts must be made so that data can be captured in a standard fashion throughout as much of the world as possible so that it can be interchangeable and so that studies being done in France, Germany or Italy can apply directly to the approval process in the United States. By the way, it is my experience in reviewing certain drugs which are approved in Europe and in working with them in the United States that the FDA has been quite appropriate in its frequently jaundiced view of some of these products. It seems to me that we have indeed been more appropriate here than in many other countries world-wide

and that the consumer and general population's safety is better maintained here than in many foreign countries. However, there are frequently good studies that can be applied to the approval process and we would benefit greatly by the ability to transfer data from many of the studies done abroad.

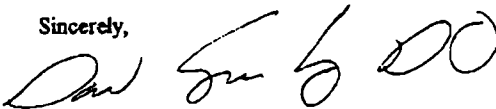
On some occasions, pharmaceutical companies may be presented with a drug that is truly innovative and perhaps lifesaving if patients were given the opportunity to benefit from this product. A process must be put in place to expedite these drugs while at the same time not losing the necessary data that one would need to analyze risk versus benefits. Therefore, I would like to suggest that in these unique cases, a decision be made to switch a product from a close label double blinded protocol to a open-labeled protocol where the drug can be more widely distributed and studied while it is continuing to be carefully monitored.

In the same vein, I would like to suggest that we diligently pursue the potential for long-term phase IV studies (or those studies which take place post approval). As I stated earlier in this report, it frequently takes at least a million doses of a drug to develop an adequate side effect profile. We must, therefore, extend the monitoring process into the post approval phase and establish good standardized criteria for doing so as well. This needs to be done in the format of actual organized clinical trials demonstrating not only a side effect profile but efficacy.

To summarize, I would like to suggest that the FDA, has been most appropriate in charting a course through very treacherous waters. To further aid their efforts, I would suggest increased standardization in both the review process and the monitoring process. Also, I would like to see a network of local medical experts involved as the study proceeds reviewing it concurrently not in a retrospective fashion. Again, I think that we are truly in many senses an international medical community and attempts to collate and organize data on an international level would be to everyone's benefit.

Thank you very much.

Sincerely,

A handwritten signature in dark ink, appearing to read "David O. Ginsberg". The signature is fluid and cursive, with the first name "David" being more prominent and the last name "Ginsberg" written in a more compact, stylized manner.

David O. Ginsberg, D.O.
President, Concorde Clinical Research, Inc.
Associate Professor, Family Practice, Philadelphia College of Osteopathic Medicine
Director of Research, Philadelphia College of Osteopathic Medicine

Mr. FOX. Did you want to proceed? Please identify yourself and your affiliation.

Mr. BOEHRINGER. My name is John Boehringer. I am president and owner of Boehringer Laboratories. I appreciate Congressman Fox hosting this hearing here.

I grew up in Congressman Walker's territory and went to school there. My home and my plant, my manufacturing facility, are in fact 2 miles down the road here.

Mr. FOX. Thank you for coming.

Mr. BOEHRINGER. I would like to bring out a little heard voice here today from the small device manufacturing companies. We heard of the billion dollar activities, but we started in my basement. After a career in engineering, I worked at the University of Pennsylvania to develop some devices, five of which ultimately ended up on top of Mount Everest in the University of California's scientific research project.

More recently, if you have a hip or a knee replaced, we are the leader in blood collection equipment to replace your blood as your knee and hip are being replaced.

I will make a statement unequivocally today that I could not start my company today in the environment that we have with the FDA and the regulatory environment that we face. To me, as an American citizen that is a very sad thing.

We are already started in business, so that aspect of it only slows me down, but the people that are coming along and keeping our industry alive—we have not seen any competitors, for example, in suction equipment. There were eight 10 years ago. There are three today.

In blood collection and reinfusion, which is extremely important given the blood supply situation, there are about eight of us now. I predict in 5 years there will probably be three of us.

To give you an idea on the FDA regulations, just to give you one horror story, we had to requalify polyethylene. A small company here in Norristown, PA, had to go to the FDA and requalify the use of polyethylene, which is probably used in millions of devices, before we could get approval.

That meant that we had to spend the money for an independent lab. We had to wait for the approvals. We had to wait while they advanced our application so we could get that done. It was just a tragedy is what it was. It delayed us for over a year in bringing this blood supply equipment to the market.

I have four recommendations coming out of this that I would like to suggest.

One of the things that is happening to all of us is a subtle thing but it is very effective, and that is the measurements that the FDA are reporting to you in Congress about reduced backlogs is nonsense. What they measure in backlog is not from the time that we submit. They measure backlog from the time we resubmit. If there is any sort of delay or anything that they measure, they are measuring from the latest resubmission.

When they sent us back to requalify polyethylene, they started measuring the backlog from the time we resubmitted that application. This goes on and on and on. This is not an isolated incident.

We have over 30 patents as a small company in the fields that we work in. I can almost say it is easier to deal with the Patent Office than it is with the FDA. I am the last person in the world that wants to ship an unsafe or a nonefficacious product to my customers. That is as a human being and also as a businessman. I really do not need the FDA to discharge that responsibility for me.

I would like to make four recommendations, if I could. One: Long ago in quality control manufacturing we learned that some vendors are safer and better than others, and we relaxed inspection on those vendors. Ford, Chrysler and GM even have approved vendor lists that they accept the vendor's certification for what they are receiving.

There are so many of us with an absolutely clean record with the FDA that it seems to me that they could ease the inspection criteria on our companies for new product approval based on the fact that we have clean records.

They typically have what I call "an organized for the gangster" mentality. The rules are set for the absolute worst felons in our society, and then the other 95 percent of us who are trying to do a good job as human beings and citizens are governed by that "gangster mentality" rule. I would say let us use a graduated approval process that recognizes 25 years of safe operation.

The second thing that I would like to see is an enforced time and clock accountability so that they cannot reset the clock from resubmission. When a product submission goes in, they should share some of the responsibility for the backlog and delay that they are forcing on us. They should start measuring from day one instead of from each resubmission.

The third thing I would like to see is a mission written into the law that says the FDA has a responsibility to assist U.S. manufacturers. They look on us right now I think as someone they have to enforce against. I really believe that they feel very little responsibility for the health and safety of the industry that they are regulating.

The fourth thing that is a most dangerous thing that we see in devices which the previous gentleman referred to is the application of drug law mentality enforcement to device manufacturing.

I wrote to the FDA and helped write the good manufacturing practices back in 1976-77, which I am happy to say many of the suggestions I made were incorporated. They wanted us to save one instrument out of every lot that we made just as they asked SmithKline to save one pill out of every lot that they made. The only difference is the pill costs \$5. A spirometer costs \$950. Merging the two mentalities leads to dangerous policy.

One of the things that we are being asked to do now is report and document the invention process. That is going to lead us right down the route of the AEC and NASA and all the other innovation areas that have been killed in the United States. By the time you get around to documenting an invention as a device manufacturer, you may have more money in the invention than the gross sales of that device will be for a year or two.

I am proposing those four things.

Mr. Fox. Thank you for your commonsense suggestions, as well as the other doctors who testified.

Could you give your name for the record and your company again?

Mr. BOEHRINGER. John Boehringer, B-O-E-H-R-I-N-G-E-R, Boehringer Laboratories, Inc., 500 East Washington Street, Norristown, PA.

Mr. FOX. Right here in town. Thank you very much, Mr. Boehringer.

Chairman Clinger, did you have any questions for the witness?

Mr. CLINGER. No.

Mr. FOX. If we have other witnesses who wish to testify, please come forward and identify yourself. We will be happy to have your testimony.

Ms. DELUCA. Hello. Thank you for allowing me to speak. I am Barbara DeLuca. I am the executive director for the Linda Creed Breast Cancer Foundation.

I am speaking on behalf of 2,600,000 million who have been diagnosed with breast cancer. I must tell you that two of those young women I attended funerals for this week. Too many women of all ages are losing their lives to breast cancer.

In the last 30 years, nothing has changed in the way breast cancer is treated, with the minor exception of some hopeful new drugs that have appeared on the market, Tamoxifen being one of them, Taxol being one of them, and Taxotere hopefully could be one of them.

When a women is in the last throes of her disease, Taxol has been the one hope. I know one woman who had given birth to a child and then was able to have her life extended for 1 full year because of Taxol.

We are hopeful to see new drugs coming onto the market. In the last few years, because of a grassroots movement, women across the country have been fighting for new funding for research. That money has increased slowly. That money has not increased enough, and we are hoping that it will not be cut in the next few weeks because it is so desperately needed.

When drugs are discovered with those new research funds, we hope that they will come to fruition and come to the market with all safety measures having been taken, so that women will have the choice of having their lives saved by new drugs that are being brought to us.

I thank you very much.

Mr. FOX. Your last name again?

Ms. DELUCA. DeLuca.

Mr. FOX. And you are local? What is your—

Ms. DELUCA. I am with the Linda Creed Breast Cancer Foundation that is located in Philadelphia.

Mr. FOX. I would like to say first of all, thank you for your poignant testimony. We are very familiar with the Linda Creed Foundation.

We have spoken out in recent weeks in the Appropriations Committee to try to fully fund the women's healthcare initiative. As well, we had a witness today who was supposed to speak just to what you talked about with the drugs not yet approved, Taxotere, except that she had chemotherapy yesterday and was so debilitated that she could not be here to speak to us.

Ms. DELUCA. Yes, and I know Beverly well from our National Breast Cancer Coalition.

Mr. FOX. I appreciate your testimony.

Ms. DELUCA. I thank you for your help, and I hope everyone will continue to fight for this funding.

Mr. FOX. That is our hope, too. If you have anything in writing that you want to submit to us beyond your oral testimony which has been transcribed, we would love to receive it.

We will make sure that you get our address so that we can include it in the record because this is the very reason why we have created this hearing so we can change the FDA law.

Ms. DELUCA. I certainly shall. Thank you.

Mr. FOX. Thank you, Barbara.

Are there other witnesses who wish to come forward to testify at this hearing at this time?

Chairman Clinger, do you have questions you want to ask of any members of the panel who just finished?

Mr. CLINGER. No, Mr. Chairman. I would just again commend you for being the instigator for this hearing. I think we have had a very thorough hearing. As you say, we have had some very compelling testimony. I think it is going to be enormously helpful to us as we go back and begin to deal with legislation in these areas.

One of the functions of this committee which I chair, which is the Government Reform and Oversight Committee of which this is a subcommittee, is to really figure out how we can make the Government work better and work more efficiently instead of being sort of a mindless, senseless bureaucracy responsive to our customers. Our customers are the people who depend upon these agencies.

Certainly FDA is a prime example of where we can do so much more to provide help for people who are in desperate need of that help. I think we all will leave this hearing rededicated to making this thing work better and work more efficiently.

Again, I just commend you for bringing us to Pennsylvania and holding this hearing.

Mr. FOX. Thank you, Mr. Chairman.

I just wanted to say to all of our doctor witnesses, Dr. Jungkind, Dr. Cionci, Dr. Sperling, Dr. Sklaroff and Dr. Fisher, that each of you has given to us very poignant testimony which I think goes to the heart of the fact that we need to make sure that patient concern, especially those who need the life extending drugs and the lifesaving drugs, in fact do receive those drugs as soon as possible. We need to accelerate the acceleration process, if I can say so.

It is the work of the many advocates here for healthcare that have caused us to draft the proposal, which will be known as, after we receive your testimony and we have had a chance to digest it, the Life Extending and Lifesaving Drug Act of 1995, which will in fact be, from our perspective, an improvement on the existing Food and Drug Administration law.

We need to breakdown the barriers to experimental drugs. We need to approve new drugs as fast as possible. We need to increase the flow of information to consumers about drugs. We need to reduce the number of duplicative regulations that have restrained us in serving our patients and constituents, and we need to make sure

that FDA is not fostering delay of approvals, but in fact facilitating drug access.

We hope that the combined wisdom of those who hear this testimony, and I want to thank especially also David Samowitz and his mother who gave poignant testimony which was excellent. I appreciate his courage in coming forward and speaking for those who could not be here. You really are the human element behind why we are here. We wish you the best in your life career. If we can help as Members of Congress to move that along, we hope you will call us on a personal basis.

Frankly, we are all appreciative of those members who were here. The members of the committee that Mr. Clinger chairs who could not be here will be receiving that testimony formally, and we very much appreciate all that you have done and will do to move us forward here in the United States to take care of our patients.

We thank you very much. If there is no further testimony, I will formally adjourn the meeting. Thank you for coming.

[Whereupon, at 1:55 p.m. the subcommittee was adjourned.]

