Jerry Mendel
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TALKING POINTS ON FDA LEGISLATION
(For conversations with Senators Mikulski, Harkin and Dodd.)

- Markup today on Senator Kassebaum's FDA legislation. The House Republicans will introduce their bill today.

- FDA critical to protecting safety of food supply, blood, drugs and medical devices.

- President has been extremely successful in drawing line between Democrats and Republicans on basis of public health. Republicans have been hurt by their efforts to weaken environmental protections. FDA legislation in Senate and House likely to be a very public fight. We need to be able to continue to draw this line.

- The Administration's strategy has been to be very aggressive in undertaking administrative reforms, but to fight Republican legislation that undercuts basic health and safety requirements.

- I am very concerned that Democrats not give the Republicans cover on this issue. Therefore it is critical that the democrats stick together.

- Otherwise we will lose our leverage. Muddle our message. Will end up on the other side of patient groups and other consumer groups.

- Urge you not to break with the other democrats. That way if there is to be FDA legislation, we will have maximum leverage in any negotiations.

For Senator Mikulski: I am particularly concerned about the message your vote sends to women groups -- who have in mind the Dalkon Shield and DES disasters. There products who how important it is to keep the basic safety and efficacy requirements strong..

Make strong commitment to work w/ Senators on an acceptable alternative bill.

TELEFAX TRANSMITTAL SHEET

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DATE: 2 April 1996

TO: Elizabeth Drye

TELEFAX NUMBER: 202-456-7028

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THE FDA REFORM MARKUP (Senate - March 29, 1996)

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Mr. KENNEDY. Mr. President, today when Americans get up in the morning and brush their teeth, they do not think about whether the toothpaste they are using is safe. When they eat their breakfast they do not think about the safety of the food they are eating. When they take a pill to treat an illness they do not worry about whether the drugs are safe. They do not worry about whether those drugs work. Americans have confidence in all of these products because the Food and Drug Administration is an independent agency with enormous credibility.

Yesterday, the Senate labor and human resource committee approved a **FDA** reform bill, S. 1477, that will destroy that confidence. S. 1477 will cripple the **FDA** , and turn many of its functions over to private industry.

The history of food and drug legislation is that we have learned from the tragedies of the past. The United States was

fortunate to avoid the Thalidomide tragedy in the 1950's. But in the 1950's and 1960's, we did not avoid the tragedy of DES, Diethylstilbestrol, which causes cancer in the daughters of women who took it.

In the 1970's we did not avoid the tragedy of the Dalkon Shield, which caused thousands of cases of infertility in women who used it. In recent years we did not avoid the tragedy of the Shiley Heart Valve which broke and caused many deaths.

As a result of the Thalidomide tragedy, we strengthened our drug laws in 1962. As a result of the Dalkon Shield tragedy we strengthened our medical device laws in 1976 and we strengthened them again in 1990 after the Shiley valve tragedy.

Most recently, we reduced the delays in approving prescription drugs with user fees. As a result, we are now approving drugs faster than the United Kingdom. We have fixed the drug lag. In fact, the United States approves more important new drugs faster than any other country in the world.

But equally important, we have the best record in the world of blocking the approval of unsafe or ineffective drugs that have to be withdrawn after patients have been killed or injured.

The bill reported from the committee goes in the wrong direction. The lessons of the past have been turned on their heads, and those who have failed to learn from the history of Thalidomide, Dalkon Shield and DES, will condemn the American public to new device and drug tragedies. The basic theme of the legislation the committee approved is privatization. It says, `let us return to the days when drug manufacturers decided what was safe and effective.' It says, `let device manufacturers pay private bodies to determine if their heart valves and pacemakers will help or harm patients, instead of relying on the scientists at the **FDA** , who have no interest except the public interest.' If this bill is enacted into law, the Food and Drug Administration will no longer have the principle responsibility for making critical decisions about the safety of the food supply and the safety and effectiveness of drugs and medical devices. Instead, those decisions will be made by private companies.

In the cases of medical devices, those companies will be selected and paid by the medical device industry to decide the safety and effectiveness of the products. No company that is paid to do product reviews can be objective, if future business depends on whether it grants a favorable decision. And to make the conflict of interest even more blatant, it will be up to the regulated industry to determine how much compensation the regulator will receive for the review.

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Do you get this? That the medical device company will make the judgment as to which individual will come and inspect their particular medical device, and they, the inspector and the company, will work out the terms of payments.

If you were one of those inspectors, how long do you think you will make adverse judgments against those companies if you ever expect to get paid or hired again? You have a basic, fundamental conflict of interest. Compare this with the current situation where an inspector has no financial interest in making the judgment and bases decisions only upon pure science. That is how we do it at the present time.

As I said, we do it very successfully with regard to drugs and biologicals. It is slower with regard to medical devices, and various animal vaccines. We grant the **FDA** has not done well enough. But over the 30 years that our committee has been reviewing how to speed up the **FDA** , we have only been successful with one major change and that is when we put on the user fees, with the support of the pharmaceutical industry, with the support of President Bush, and with the support of Congress. And we have seen a dramatic change in terms of performance, in the approvals; significant reductions in terms of the considerations of those items. It has been successful. Now we are about to tamper with that particular effort, which has been reviewed by GAO, and by the Tufts Medical School, which has been constantly critical of the **FDA** , but all of them say that this is a program that is working.

It is not working as well in the device areas, as I mentioned, but what we are doing, I believe, is putting seriously at risk the successful programs that have been enacted in recent times.

In Britain in the last few weeks, we have had a stark demonstration of what can happen when the regulatory body charged with protecting the public interest has a conflict of interest.

Britain is in a food safety crisis over the meat from cattle with mad-cow disease because the Government paid too much attention to commercial interests and not enough attention to the health of consumers. Now, because there is growing concern that mad-cow disease can be linked to a fatal disease in humans, British meat is being banned in every country in the world.

In Britain, the public is demanding to know why there is no independent body like America's Food and Drug Administration to protect the public. That is the question on the minds of British consumers.

How ironic that just a few days after the mad-cow disease disaster came to light, legislation was approved by our committee to dismantle the regulatory agency that is universally recognized abroad as the gold standard for the world. The **FDA** is our strongest defense against this kind of crisis in the United States. We have the safest food supply and the safest medical products in the world. We should not take any steps that jeopardize the confidence of American consumers in the safety of food and medical products. Yet this bill would seriously weaken current protections.

In addition to privatizing review of medical devices, this bill tells the public to trust drug manufacturers to make changes in the manufacturing process without **FDA** review to determine whether the changes affect safety or effectiveness. Companies under pressure to increase profits sometimes put profits first or simply sometimes make mistakes. In fact, most experts believe that mad-cow disease spread throughout Britain by a change in the manufacturing process of animal feed by some companies, the kind of change that S. 1477 leaves up to American companies to decide on their own.

Under this legislation, no change in the manufacturing process would require prior approval from the **FDA** . Yet, a change in the manufacturing process can determine whether a polio vaccine prevents polio

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or causes it. A change in the manufacturing process can determine whether a blood transfusion is life saving or whether it transmits AIDS or hepatitis to the patient. An independent **FDA** is needed to protect the public against these tragedies. Commercial interests should not prevail.

Further, the bill sets excessive time limits for review with no additional resources. The **FDA** will be unable to meet these requirements and do its job.

Even worse, the bill sets the wrong priorities so that every `me-too' drug of little additional therapeutic value receives the same priority as urgently needed new cures, and if **FDA** cannot meet the unrealistic time limits in the bill, the agency is required to contract its responsibility out, leading to further unacceptable privatization.

What did we do in the earlier legislation? We said on the priority drugs, we are going to make sure that these are going to be addressed within the first 6 months and then those that are of lesser significance and importance within 12 months. Therefore, the **FDA** is able to use some discretion in the areas of breakthrough drugs. The last drug on AIDS was only about 2 1/2 months under review because **FDA** had worked with the company further up the line to accelerate the consideration and the whole development time.

So **FDA** has been moving in the area of priority drugs. Now what does the legislation say? The legislation says you have to examine all of them, all of the drugs within the 6 months. The fact of the matter is, as anybody who understands what goes on out at the **FDA** knows, the vast majority of those other drugs are `me-too' drugs, not the breakthrough drugs.

So now instead of bringing focus and attention of the gifted and able scientists out at **FDA** on those drugs that could be

breakthrough drugs in cancer, in AIDS, in hepatitis, in all kinds of diseases, we are going to divert their attention to looking after the `me-too' drugs that can make extra bucks for the pharmaceutical companies. Is the public interest served there? It is not.

This is a direct result of the pharmaceutical companies wanting to get some additional attention so that they can put on the market and promote and advertise and make additional profits from those `me-too' drugs. This is unwise, ill-conceived, and bad health policy. Mr. President, we all know that when the Congress previously acted in a bipartisan way with the Executive together with the pharmaceutical companies, all of them working together, setting the goals, setting the standards, setting the accountability on what the **FDA** should do--96 percent of the goals that were established were achieved, and now we are saying, `Well, that isn't good enough. That isn't good enough even though the GAO says we are the best in the world. That isn't good enough, and we are going to change that system,' alter that system in a way which I think diminishes the efficiency of the **FDA** and could very well diminish the opportunities of moving the breakthrough drugs to the consumer in a more orderly, effective, and rapid way.

Mr. President, I was talking about the changes in both time limits for the consideration of priority drugs and also about the changes in the manufacturing processes that do not have to have prior approval by the **FDA** .

FDA is the most respected regulatory agency in the world. With too few resources now, **FDA** still gives us the safest food supply in the world and the best medical products. The **FDA** seal of approval is accepted with confidence and trusted worldwide. American companies benefit immensely from that confidence. This bill will turn that seal of approval into a label that cannot pass the truth-in-advertising test. Whether the product is heart valves or blood derivatives or vaccines or food, the American people

will be at risk.

There are ways that **FDA** should improve. Some products do need to get to market faster. **FDA** should collaborate as much as possible with companies and researchers to reduce the time of bringing safe and effective products to market. They are doing a good job now; they ought to do a better one. But we should not gut **FDA** 's independence or the laws that give it that independence.

This legislation puts the commercial interests of companies ahead of the best interest of consumers. I am hopeful, Mr. President, that the provisions of S. 1477 that undermine health and safety can be revised before the bill comes to the floor. I know that Senator **Kassebaum** is committed to working with all interested Senators, and I pay tribute to Senator **Kassebaum**. She has spent an enormous amount of time herself on this issue. She has listened to different positions taken by those who are committed to the public health interests. She has listened to Members of the Senate.

I have the highest regard for her and the way that she has conducted the hearings and the leadership she has provided in this area, but I do find that I come out on a different side than she does with regard to the bill itself.

The present bill would destroy the safeguards protecting the American people that have been built up over the decades. It will cripple the world's best regulatory agency. It would be tragic if it became law. When the American people understand what is in it, I believe they will reject it.

Mr. President, I yield the floor.

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Mr. INHOFE addressed the Chair.

The PRESIDING OFFICER. The Senator from Oklahoma.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

DAVID A. KESSLER

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

FEBRUARY 21, 1996

FOR RELEASE ONLY UPON DELIVERY

TESTIMONY OF DAVID A. KESSLER, M.D.

Good morning, Madam Chairman. I am pleased to be here and want to thank you for holding this hearing on this very important public health issue. Today we are here to discuss how the Food and Drug Administration (FDA) can do the best job possible in protecting and promoting the public health.

INTRODUCTION

As we explore that question, it is important to acknowledge that we share the same goals. I know, Senator Kassebaum, that you and members of the Senate Labor Committee understand that American patients are best served when they are assured that the medicines they take are safe and really work, that American patients are most helped when they are assured that medical devices are safe and really work. The rigorous demand for safety and efficacy that makes FDA approval the international gold standard is, in fact, in the best interests of American patients. Likewise, FDA shares with you the belief that timely access to new drugs and devices that are shown to be safe and effective is an important

measure of how well the Agency protects and promotes public health in the United States.

If we are to achieve our shared goals of improving the Agency's ability to protect and promote the public health, we must base our work on FDA's current performance. Unfortunately, too many of our critics justify the call for "reform" based on how the FDA did its job in the 1980s or earlier. They have missed the substantial progress that the dedicated doctors, nurses, engineers, chemists, microbiologists, biostatisticians, nutritionists and others at the FDA have achieved over the past several years. They would have us ignore the important lessons we have learned about the kind of change that will result in getting safe and effective drugs and devices to the market more quickly. Those who fail to recognize the Agency's performance and achievements threaten -- intentionally or not -- to undermine the real progress the Agency has made. Undermining progress in critical public health and consumer protection is not "reform."

THE FOOD AND DRUG ADMINISTRATION IN 1996

MEETING AND EXCEEDING THE PRESCRIPTION DRUG USER FEE PERFORMANCE GOALS

According to the General Accounting Office (GAO), the average approval time for new drug applications (NDA) submitted to the Agency in 1987 was 33 months. For NDAs submitted in 1992 the time had been reduced to 19 months. These improved approval times have been made possible by shortening the time for completion of most first reviews to only 12 months. How did we do it? Congress, the Agency, and the pharmaceutical industry recognized that additional resources were one key to improving FDA's review of drugs and biologicals, and Congress enacted the Prescription Drugs User Fee Act of 1992 (PDUFA). The Agency, in turn, committed to very aggressive performance standards, with higher hurdles in each succeeding year until full implementation in fiscal year 1997. These performance standards were negotiated with and agreed to by the pharmaceutical and biotech industries.

We already have achieved one of the major 1997 performance goals. We achieved it in fiscal year 1994 -- a full three years ahead of schedule. For the drugs submitted to FDA in fiscal year 1994, we

reviewed and acted upon 96 percent of them on time. In most cases, that meant first action within 12 months.[1]

This improved performance has been validated by GAO. At the request of this Committee, GAO looked at how FDA was performing even before PDUFA was enacted. GAO found that review and approval times for new drugs have been reduced dramatically. In addition GAO found that by 1994, FDA review and approval times were faster than those in the United Kingdom -- a country many critics like to cite as a way of doing things better and faster.

We should never forget that the ultimate goal is ensuring American patients have access to world-class medicines. By that measure as well, the FDA is delivering. The story of AIDS therapies is especially telling. Of the six antivirals used to treat AIDS, FDA was first to approve them in five instances, DDI, DDC, D4T, 3TC and Saquinivar. In the case of AZT, FDA acted contemporaneously with France and the United Kingdom. Two of the newest and most promising AIDS therapies will be considered at an FDA advisory committee next week, and we will be the first

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[1] If a major amendment is submitted by the manufacturer late in the process, an additional three months is granted.

country to do so. But the story goes beyond AIDS. Taxol for ovarian cancer, Fludarabine for lymphocytic leukemia, Pulmozyme for cystic fibrosis, Betaseron for multiple sclerosis, Riluzole for Lou Gehrig's disease, and Cognex for Alzheimer's were all first approved in the United States.

FDA IS A WORLD LEADER IN DRUG APPROVAL

One measure of FDA's drug review performance is found in how we compare to the performance of other major regulatory agencies around the world. We looked at the United Kingdom, Germany, and Japan and found we compare very well. First, there are numerous drugs with important therapeutic values available here but not in these other countries. Second, virtually all of the drugs available in these other countries but not approved here have therapeutic equivalents in the United States. Third, the United States is first to approve a significant proportion of "global" drugs -- those ultimately approved by more than one country. Finally, we have a strong safety record.

These conclusions are based on our analysis of the "new molecular entities" (NMEs) introduced anywhere in the world between 1990

and 1994. We looked at when those drugs were approved here and in Germany, Japan and the United Kingdom -- four countries that account for 60 percent of global pharmaceutical sales. Let me just give you a brief glimpse at the numbers in the FDA study, "Timely Access to New Drugs in the 1990s: An International Comparison." There were 58 drugs that had been approved in both the United States and the United Kingdom. We approved 30 of them first, the United Kingdom 28. When we approved a drug first, we did so by an average of 17 months before the United Kingdom; if they approved first, they were ahead by an average of 15.8 months. There were 44 new drugs approved in both the United States and Germany. We approved 31 of them first, Germany 13. When we approved a drug first, we did so by an average of 17.9 months before Germany; if they approved first, they were ahead by an average of 10.8 months. There were 14 new drugs approved in both the United States and Japan. We approved 10 of them first, Japan 4. When we approved a drug first, we did so by an average of 22.4 months before Japan; if they approved first, they were ahead by an average of 18.5 months. If you are an American patient, you have access to therapeutically important new drugs sooner than any other country's citizens.

MAKING NEW PRODUCTS AVAILABLE SOONER

In addition to shortening review times, the Agency has developed a number of innovative and well accepted mechanisms that give seriously ill and dying patients access to potential therapies before they are approved for marketing. We recognize that this approach has its risks. But we also recognize that when it comes to getting needed therapies to terminally ill patients, the riskiest thing we can do is to be unwilling to take risks.

We have instituted innovative pre-approval policies, such as the "treatment IND," under which patients may get access to a promising drug after clinical testing shows that it may be effective, but before it is approved for marketing. We also have developed a process to accelerate approval of drugs for serious and life-threatening diseases, by approving such drugs for marketing before the data from traditional clinical trials are complete, if the drug shows an effect on a "surrogate marker." A surrogate marker is a laboratory measurement, such as an increase in the number of CD4 cells in a person with HIV, that is used to predict actual clinical outcome, such as longer life.

IMPROVING DEVICE REVIEW TIMES

Improvements also have been made in the times for the review and approval of medical devices. With respect to the so-called 510(k) process, through which 98 percent of all medical devices evaluated by FDA reach the market, the average review time in fiscal year 1995 was 137 days, down 24 percent from the 184-day average in fiscal year 1994. The average review time for those devices needing premarket applications (PMAs) is still too long, but we are making progress there as well. The average PMA review time in fiscal year 1995 was 20 months.

It is important to remember, however, where the Agency was in the 1980s. Congress found -- as did the Agency itself -- that the scientific and medical standards for the review of medical devices were lacking. FDA looked at devices the way an engineer would; we did not focus sufficient attention on whether the device would actually make the patient better. Congress told us to do better, and we have. The clinical standards for medical device reviews have been bolstered significantly, and now we are hard at work on reducing the review times.

IMPROVING ANIMAL DRUG AND FOOD ADDITIVE REVIEW TIMES

Although most of the discussion of FDA reform focuses on the human drug and device review processes, the Agency also has significant responsibility for the review and approval of animal drugs and food and color additives. The American food supply is one of the safest in the world. The premarket determinations that animal drugs are safe and effective, especially when they are intended for use in food producing animals, and that food additives and color additives are safe constitute critical links in the food safety chain.

As is the case with human drugs and devices, the Agency has recognized the need to improve the timeliness of the product review processes in both these areas. In the new animal drug area, approval times that had steadily increased between 1988 and 1994 have begun to decline. This is particularly significant given the changing nature of the types of applications being submitted to the Agency. Five years ago, a large part of the applications were for combination feed drugs. These consist of two or more drugs already approved for specific indications and species. Today, we are receiving many more applications for new

chemical entities, new species or new applications. As a result, the complexity of the applications has increased considerably.

The Center for Veterinary Medicine (CVM) has developed procedures to facilitate the development of better applications and to expedite the review process. Through pre-Investigational New Animal Drug exemption conferences and phased submission of the technical sections of the New Animal Drug Application, CVM has reengineered the review process to decrease approval times and increase the availability of safe and effective animal drugs.

Similarly, the Center for Food Safety and Nutrition has developed a plan to increase the timeliness and predictability of Agency action on food and color additive petitions. First, in order to address the backlog of pending petitions, the agency has allocated additional resources to the program: 23 additional Agency scientists have been reassigned temporarily to the food additive program; the Agency is awarding contracts for expert review of certain portions of food additive data packages; and one and one-half million dollars have been spent on enhanced computing facilities for the program. With these efforts we will begin to see a decrease in the petition inventory.

In addition to these added resources, we instituted a threshold of regulation policy under which indirect food additives that do not present any substantial safety concerns are exempted from the petition process. The Agency processed 47 submissions under this new policy in 1995.

Here again, we recognize that one way to decrease review times is to improve the quality of the food additive petitions that are filed with the Agency. We have been working with the industry to do that. FDA personnel have begun conducting workshops for petitioners to discuss what data are needed to file a complete food additive petition.

Food additives are distinctly different than drugs and devices. Whereas drugs and devices provide therapeutic benefits to certain individuals, food additives will potentially be consumed by everyone in the population. Whereas drug and device approvals are product specific, a food additive approval results in a regulation permitting anyone to manufacture or use the additive, consistent with any patent protection and in conformance with the limitations of the regulation. These facts contribute to the unique safety concerns relating to food additives and the unique

features of the review process of food additives. We welcome the opportunity to discuss this process further at another time.

REDUCING PRODUCT REVIEW TIMES, STRENGTHENING MANAGEMENT AND ELIMINATING UNNECESSARY REGULATORY BURDENS

We have improved review times without sacrificing the high standards that give Americans confidence that their drugs are safe and work. Under PDUFA, the Agency was assured of adequate resources to do the job and the job was clearly defined through performance goals. At the same time, how to achieve those goals was left to Agency management, and accountability to Congress was assured through the five year authorization. That was real reform. Reauthorization of this program should be a cornerstone on which we build other improvements.

The progress we have made, however, is the result of much more than the additional resources available under PDUFA and extends beyond the drug review process. Of equal significance has been the commitment of Agency management to streamline and improve the way we regulate. I think we all can agree that strong consistent management, the removal of unnecessary regulatory burdens, and the elimination of wasteful or inefficient practices all serve

the critical public health goals to which we are committed. A review of the Agency's contribution to the Administration's Reinventing Government Initiative well demonstrates the depth of our commitment to improving our regulatory processes. For example, we have changed the way we regulate biotechnology products, instituted management reforms ranging from team review to greater use of outside expertise, eliminated or modified product and process reviews where the public health risks did not justify the allocation of resources devoted to those tasks, simplified and expedited the export process, engaged industry in a constructive dialogue about how to do more. We are committed to doing more, and we welcome the opportunity to work with you, Senator Kassebaum, and the Committee, and to continue working with the industry, on further improvements.

REINVENTING PRODUCT REVIEW: S. 1477 AND OTHER REFORM PROPOSALS

We appreciate having the opportunity to discuss the "Food and Drug Administration Performance and Accountability Act of 1995," S. 1477, and the impact this bill would have on the Agency's ability to protect and promote the public health. I would like

to acknowledge and commend the Chairman for her leadership on these issues. We look forward to working with you and the other members of the Committee on these important issues.

There are many sections of S. 1477 which we believe could be the basis for constructive improvements, and on which we hope to be able to continue to work with the Committee in developing strong legislative improvements. These provisions include a statement of Agency mission, specification of performance standards, changes to the export requirements, contracting-out authority, establishment of adequate reporting systems to enhance Agency accountability and the need for greater input into the guidance documents that we issue.

The general thrust of this legislation is, I believe, how the Agency can do its job better, more efficiently. We share the Chairman's concern with these issues. We heeded and acted upon the concerns you and others -- Senator Kennedy, Senator Mikulski, Senator Frist -- expressed at the hearing last April. We recognized and have addressed many areas that needed improvement. We recognize there is more to do.

As the Committee has requested, we are going to address in some detail the product review process, and whether it would be feasible to meet the review times set forth in S. 1477 without compromising our existing standards of safety and effectiveness and without additional resources. Our testimony will focus on the drug review process, although the comments generally are applicable to the other product reviews for which we are responsible. We will then address the other provisions in the bill, except for those dealing with promotion of off-label uses (Section 407), which will be discussed separately in Mr. Schultz's testimony tomorrow.

We must remember that today's drugs, and science, are not what they were a few decades ago. It may look as though what a company is doing now -- showing that a drug is safe and effective -- is the same thing it was doing decades ago. But that is not the case. What the public, the scientific community and regulators around the world expect is very different now. Until just a few decades ago, clinical drug testing was largely an ad hoc anecdotal observational art -- patients received a drug and clinicians assessed whether individual patients were helped or harmed. In recent decades, indeed in recent years, a great deal of data and understanding have accumulated regarding many

aspects of clinical development, including placebo effect, multiplicity of endpoints, post hoc analyses, surrogate endpoints, sources of investigator bias, subset analyses, effects of demographic factors (gender, age, race), drug interactions and impact of concomitant therapies. With these understandings has come a realization that both the observational approach and clinical trials which are not carefully designed, while they may correctly identify treatments whose benefits are dramatic and adverse effects are highly limited, often give incorrect impressions regarding a treatments' safety and efficacy. Thus, the old approaches often led to countless incorrect practice decisions (e.g., unnecessary appendectomy and hysterectomy, use of antibiotics for the common cold, for example.)

Moreover, there are new technologies with which we must now learn how to deal with -- xenotransplantation, transgenic animals, devices that hold biological systems inside of them, robotics, neural networks, computer guided surgery, gene therapy, and neucleic acid vaccines to name a few. We need to develop scientifically-sound ways to both protect and promote the public health in areas of explosive growth and uncertain science.

ELEMENTS OF DRUG REVIEW BY FDA

Every application submitted to the Agency purports to demonstrate that a drug is safe and effective for treatment of a specified ailment or condition. Upon independent review, however, many applications do not support an objective finding that the drug, in fact, is safe and works. The Agency's job is to conduct that independent review. The basis for the Agency's decision is the data collected by the sponsor during pre-clinical and clinical testing. We have to determine that the studies are well designed and capable of demonstrating safety and effectiveness. We also have to determine that the data on which we make our decision have integrity: that the trials actually were conducted and done so consistent with the protocols, the primary data accurately reflect the actual clinical results, and the company's analyses of the data are fair and objective. The various components of a typical drug application -- chemistry, toxicology, biopharmaceuticals, etc., -- and the types of questions that need to be answered in determining whether a drug is safe and effective are outlined in Attachment 1.

For each medical product, there must, on balance, be demonstrable net benefits that are greater than the risks. Few, if any, new

products are totally safe; so judging their safety becomes a risk-benefit decision. We must determine if each new drug or device is safe enough in view of its anticipated benefits and the comparative benefit of other available treatments. The benefits of a life-saving drug or device, where there are limited treatment options, might justify its marketing despite known risks, even when the risks involve serious injury or death. This is often the case with drug therapies for cancer. On the other hand, for lesser benefits, the risk patients are willing to accept from a drug or device goes down commensurately.

The availability for review by the Agency of the primary data on which the sponsor bases its claims of safety and efficacy is critical to the drug review process. I would like to commend the Chairman for recognizing this in her bill. Why is it not sufficient for the Agency to rely on summary data? Experience repeatedly has demonstrated that review of primary data is critical to verify, inter alia, the following: that responses of tumor and infections were correctly catagorized and were truly due to the study drug; that judgmental endpoints are supported by objective data and not subjected to bias; and, that adverse events are correctly categorized as to severity and causality by the drug. Additionally, access to primary data improves both the

quality and speed of the analysis by permitting the reviewer to confirm that each analysis included only and all appropriate subjects, perform critical analyses to determine to relationship of drug effects to age, gender, race, disease stage, concomitant therapies, and other key factors, and assess the impact of the drug on parameters that may not have been summarized by the sponsor. Thus, provision of primary data not only allows verification, it facilitates better and faster analyses of the safety and effectiveness of the drug.

Many different types of problems have been identified in the review process. For example, has the sponsor asked the right questions during drug development? A case in point involved the development of certain drugs to treat heart failure (phosphodiesterase inhibitors), when concern arose about potential adverse effects on survival. Studies were therefore conducted to examine both the symptoms of heart failure and the impact on survival. Unfortunately, it was discovered that although the drugs improved the symptoms of heart failure, they significantly decreased survival. As a result, the sponsors did not pursue approval of these drugs.

Another example of the types of problems that have been identified through the Agency's review of drug applications is found with a product known as Multishield Topical Lotion. According to the manufacturer, this lotion was supposed to be effective in preventing skin absorption of mustard gas. It was proposed for use by American troops in Desert Storm.

When FDA raised questions about the Multishield IND, our laboratories attempted to test Multishield, using the methodology the drug's manufacturer provided to us that purportedly showed the product met its IND specifications. The test results shown in the firm's batch records could not be duplicated by FDA--our chemists found the methodology simply could not work. We found that the analytical work he did and the test results he provided were fraudulent.

The purveyor of this fraud is now serving time in jail. More importantly, as a result of FDA's review, the safety of our Desert Storm troops was not endangered by distribution of an unreliable product on which they would have been relying on for protection against this chemical warfare agent.

Finally, in 1989 FDA reviewed an NDA for dilevodol, a beta blocker, that was marketed in Europe and about to be launched in the United Kingdom. Our review revealed several cases of severe liver injury that led to non-approval. Subsequently, the sponsor's review of marketing experience in Portugal and Japan also revealed several instances of fatal liver injury, and the drug was withdrawn worldwide.

Finally, we also have to determine that the company can make the drug the same every time, so that batch after batch of the drug has the same therapeutic profile. Through good manufacturing practice inspections we compare what the company puts in its chemistry and manufacturing controls section of its application with what it is actually prepared to do at the manufacturing plant.

FEASIBILITY OF S. 1477 REVIEW TIMES

FDA has been engaged in a continuous improvement effort that involves identifying ways to reduce regulatory burden and improve our ability to protect and promote public health and safety. We

believe that this criteria should be the test by which any reform proposal is measured.

The question presented by the Committee is whether it is feasible, without lowering our safety and efficacy standards, and without additional resources, to meet the review times set forth in S. 1477. S. 1477 requires that by July 1998 the Agency would be reviewing all drugs within 180 days, and priority drugs within 120 days (Sections 103 and 204). Comparable review times would be established for other products.

We have examined this question very carefully and I do not believe that the Agency could meet the product review times set forth in S. 1477, with existing resources, without compromising existing public health protection. Moreover, I believe that by focusing on further reducing drug review times beyond that agreed to in PDUFA we run the risk of undermining the progress we are making toward shortening the overall time it takes to get drugs to patients.

What does it take to review an application within four to six months? First, it takes an excellent application. With only four to six months there would be little opportunity to obtain

clarifications or additional information from the sponsor. Although every application could be reviewed exactly as it is submitted, very few applications are so complete and accurately presented as to be approvable without further discussion with the sponsor. Second, it requires having the necessary review staff, including all the various disciplines, ready to work on the application the day it comes in the door. That means other work needs to be put on hold. Third, it means companies ~~will need to~~ be fully ready to manufacture the drug -- so that FDA can start the pre-approval inspection at the same time we start the substantive review. Fourth, the shortened review times will compromise the effectiveness of advisory committees. Particularly for applications that present complex problems or involve substantial public health issues, these committees rely on the Agency to validate, and analyze and present clinical research findings. The timeframes for review and advisory committee consideration jeopardize the Agency's ability to perform this function for the committees.

The Cost of Shortening Review Times

Shortening review times to those specified in S. 1477 would adversely effect, in a number of ways, the goal of getting safe and effective drugs to consumers as quickly as possible.

First, reviewers will be unable to spend time with sponsors obtaining clarifications or answers to questions that arise in the course of the review. The only way to get the information will be through additional review cycles. That means it will take longer for drugs to get to market. The alternative, though less likely, outcome would be that reviewers will feel compelled to approve drugs based on less information, with fewer analyses and much greater uncertainty for patients and physicians about how the drug works and how safe it is. And that means we will have lowered our standards.

Second, Agency resources devoted to product review would need to be greatly expanded, and existing expertise duplicated many times over. We would need to have enough reviewers in every scientific discipline so that there would be reviewers with the appropriate expertise ready to begin a review the day an application was filed. This would mean that the Agency would need to severely

reduce work other than product approval reviews, work that in many instances contributes significantly to public health.

One of the non-product review areas that would suffer, and where the Agency is making important contributions that should reduce the time it takes to get drugs to market, is in helping companies understand in the clinical design phase what they need to do to establish safety and effectiveness. Right now, an unacceptably high number of NDAs are never approved. This means that companies are investing time and money into drugs that should be abandoned or into drug trials that do not demonstrate safety and efficacy. Through a variety of mechanisms, we are trying to help companies better understand what is required to establish safety and effectiveness. For example, we will meet with companies and review their protocols in depth, not limiting our review to the severe flaws that could stop the trial.

We also help guide entire areas of inquiry when we take the clinical efficacy issues for a disease state to advisory committees to gain a common understanding of what all companies need to do in a given area. Similarly, we are helping all companies with their drug development when we work with Japan and

the European Union on the international harmonization efforts, through the International Conference on Harmonization, so that clinical trials will be useful in marketing applications all around the world. These early efforts to address overall drug development times are likely to provide far greater value than an incremental reduction in drug review times.

Under the S. 1477 timeframes, the Agency also would be required to limit its involvement in the production and post-approval areas. Both of these are critically important to companies and patients. Drug production problems result in a number of different types of adverse consequences for patients. For example, one recent class I recall involved an albuterol spray that was contaminated with bacteria. The result was that these bacteria were being sprayed into the lungs of the people using the product. In fiscal year 1995, there were 251 product recalls. We need to be able to inspect, monitor production, and protect the public from poorly made drugs that are dangerous or of limited usefulness.

Right now we learn much about a drug after it is on the market. Clinical trials typically involve only hundreds or a few thousands of patients in carefully controlled research settings.

Once on the market, they often are prescribed to hundreds of thousands of people. The first several years a drug is on the market teaches us about events that occur in a very low rate, such as the aplastic anemia associated with felbamate, and therefore do not occur in clinical trials. We also learn about reactions related to ordinary medical use, such as the severe anaphylactic reactions caused by zomax that were related to how patients took the drug under ordinary circumstances. This knowledge enables us to adjust labeling and drug availability depending on what we learn after the drug is widely used in practice.

Shortening the review times also will adversely impact Agency programs that are not related to drugs or other product approval process, such as the safety of the blood supply, food safety and tampering, and mammography quality. Our efforts to protect the public from unsafe imported products -- whether it is botulism-contaminated mushrooms or hepatitis-contaminated human tissue, will have to be curtailed. It also will severely curtail our ability to respond appropriately to emerging public health threats, crises, or even to new areas where a little work would have a large payoff.

OTHER PROVISIONS OF S. 1477 THAT COULD COMPROMISE EXISTING STANDARDS

A number of provisions in S. 1477, in addition to the proposed review times discussed above, that we are concerned cannot pass that test. Rather than going section by section through the bill, I will briefly discuss the most significant of these provisions.

New Approval Standards: Sound Medical Practice And Scientific Studies

There are several sections of the bill that would establish new and lower product approval standards. For example, Section 407 would establish a new process for approving new uses of existing drugs that would completely bypass the drug approval process. It would establish a procedure for recognizing new uses based on medical practice. Unlike the current requirement, the bill provides that if an off-label use has existed for five years, is "common" among experienced clinicians and is reasonable based upon experience and other confirmatory evidence, that use could be included in the product's labeling. This provision moves us

away from the accepted scientific standard of evidence back toward evidence based solely on ancedotal experience. Medical history is replete with examples of products and procedures that were based on medical ancedote, not evidence, and were thought for years by most clinicians to be effective, but later turned out to be useless and sometimes even dangerous. Indeed, when the FDA worked with the National Academy of Sciences National Research Council to review the effectiveness of drugs first sold in the U.S. before the effectiveness standard was set in 1962, 1,124 of 3,443 drugs on the market, being marketed for various claims, were pulled from the market because they were not effective.

We are not saying that individual clinical judgments about individual patients should not be made. They are necessary and appropriate on a patient-by-patient basis. But to base drug and device labeling on such a "pattern of practice" standard would be offering the public far less protection than it has today. It also could have the unintended consequence of becoming a disincentive for companies to collect the data necessary to demonstrate whether off-label uses are effective.

Similarly, Section 702 would virtually eliminate approval of devices for specific uses. It would for the first time recognize any use "included within a general use for a predicate device" as an approved use for 510(k) devices. If enacted as is, this provision would allow a device originally marketed for one clinical indication to later be marketed for other indications, even high risk ones, with only the submission of an abbreviated application (510(k)) that would not document the product's effectiveness for the new indication. Suppose, for example, that a cardiac catheter were originally approved for mapping the electrical activity of the heart. After it is on the market, it is offered for a new use: to save lives by preventing a fatal disturbance of the heart rhythm. Under the bill, it is unlikely that we would be able to ask for data showing whether the catheter worked to save lives or was just a costly and failed false hope. Even worse, if the catheter were to work some of the time, in some kinds of patients, there would be no assurance of clinical data, independent review, or accurate labeling to help doctors sort out who are those patients where it is most likely to work, or most risky.

Furthermore, Section 703 would require the Agency to accept scientifically sound studies in lieu of well-controlled clinical

trials for medical devices. Although the phrase "scientifically sound studies" is not defined, it is assumed that what is intended is something less than well controlled clinical trials. In our view this could turn modern day science on its head by instituting a preference in law for lower quality scientific evidence, such as anecdotal reports and case studies in lieu of controlled trials. In essence, this would reverse the most significant component of the 1962 Act, the requirement that sponsors establish that products work before they can be marketed.

We understand that controlled studies are not the only way to show that a drug or device works and they are certainly not the only way used today. But, there is essentially unanimous agreement in the scientific world that they are stronger evidence than the alternatives in this bill. In every case, the Agency would have to assume the burden of not only specifically asking for good science in the form of well-controlled data, but would have to explain why it was being required in lieu of the lower standard.

We agree that a problem exists with the extent to which drugs and devices are being used for indications that have never been

approved. Some of those uses likely are beneficial. We know there have been some that were deadly, even though they were thought to be sound medical practice. The solution to this problem, however, should be one that results in the collection and review of the necessary data to establish efficacy, not one which will undermine the efficacy requirement. We would like to work with the Committee on developing those solutions.

We also are concerned that the bill would eliminate FDA's role in assuring that modifications made to a product do not adversely affect its safety and effectiveness. Under the bill, unless the manufacturer's own data show that safety and effectiveness were to diminish, FDA could not require data on the modified product (Section 702 and 707). Yet we know such modifications can carry initially unrecognized risk. Take the case of the soft tissue fixation device used in orthopedic surgery, the device was on the market to be used to anchor soft tissue during shoulder surgery. The manufacturer wanted to change the materials being used and modify the design. After reviewing the data for the proposed modifications, the Agency asked the manufacturer to perform clinical trials. The study showed that the head of the modified device often broke off after the surgery and lodged in the shoulder joint, causing severe pain and often the need for

corrective surgery. Further, the modified device could form the basis for new use claims and, as I described previously, there would be no way to assess the scientific basis for the new claims.

We are equally concerned that the bill would remove even the basic assurance that most new devices will be well made. Under Section 702 a company, even one with known manufacturing problems directly relevant to its new device, would have to be given marketing approval even though the Agency has evidence the firm is unable to produce a quality product.

Eliminating Consideration Of Comparative Effectiveness

Another area where the bill would decrease the protection of the FDC Act involves consideration of comparative effectiveness. Although the Agency generally does not base its approval decisions on whether one drug works as well as another already approved therapy, there are circumstances where such considerations are very important. For illnesses with significant public health implications, such as measles or sexually transmitted diseases, it would be unconscionable to

allow marketing of drugs which are less effective than existing therapies. For example, for products intended to treat gonorhea, the Agency requires a 95 percent efficacy rate. Similarly, vaccines for measles or other highly contagious diseases must be as effective as possible. The same consideration exists for therapies for the treatment of serious or life-threatening illnesses.

For both devices and drugs, the bill apparently would prohibit the Agency from considering uses for which a product could be marketed, unless those uses are explicitly included as label claims (Section 408). It appears this section would even prohibit the Agency from looking at clinical outcomes resulting from use of a device -- for example, whether patients with artificial hearts did well or died -- unless the outcome is part of an explicit label claim.

Section 408 also might prohibit the Agency from requiring sponsors to include in their labeling information about indications for which the drug should not be used. One of the advantages of clinical trials is that they often provide information about when a drug should not be used, as well as

information about when it works. Requiring a sponsor to include such information in the labeling can prevent very serious injury. Similarly, restricting the Agency's ability to use information it obtains from adverse reaction reporting and other types of post-marketing surveillance does not make sense.

Fentanyl is a powerful painkiller that was approved for use through a transdermal patch for pain control in patients, such as those with terminal cancer, who had developed a tolerance to opiods. Physicians and dentists began using the patch for conditions like post operative pain, in persons who were not opiod tolerant. This caused severe respiratory distress in some patients, and resulted in several deaths. Based on this experience, the Agency required the sponsor to make significant labeling changes and to include in its labeling a specific warning about this dangerous, unapproved use. Obviously, the sponsor never intended that its product would be used on patients who could not tolerate such powerful medication. Section 408 could limit the Agency's ability to include this type of important information in product labeling.

Substitution of Judgment: Third Party Approvals And Other Mechanisms To Bypass FDA's Decisions

There are a number of provisions throughout the bill which would allow companies to market products without FDA approval, if the Agency fails to meet review deadlines. Under Section 404, for example, a company that has obtained a European Union approval could market its product without FDA approval if the Agency fails to meet the review time.

The underlying rationale for such provisions appears to be that they would serve as a mechanism for holding the Agency accountable for its performance. The problem with them, however, is that they allow the concept of accountability to completely override the statute's primary objective that drugs and devices be proven to be safe and effective before they can be marketed. Although we fully agree that the Agency must be held accountable for its performance, this can and must be accomplished without sacrificing existing protection.

The concept of marketing approval by default is not new. Prior to the 1962 drug amendments that required sponsors to demonstrate that their products work, drugs could be marketed if the Agency

failed to act within specified time frames. Proponents of the amendment to require an affirmative determination by the Agency of safety and efficacy as a prerequisite for marketing approval recognized the critical importance of the Agency's review, and the need to give the Agency greater flexibility in light of the volume of new drug applications, the increasingly more complex nature of such applications and the availability of expert personnel to review those applications.

These same factors motivated Congress in 1990 to change a similar marketing approval by default provision in the device statute. As a result of those changes, the Agency must make an affirmative finding of substantial equivalence for devices to be marketed under the 510(k) clearance process. This change, like that in 1962 for drugs, enhanced the protection afforded the public.

The reliance on approvals by other countries does little to ameliorate the problem. Assuming that a drug or device legally marketed in the European Union should be marketed here simply because of the passage of time places an extraordinary faith in an untested, unevaluated system still in its infancy. Under these provisions, we are concerned that the only way FDA could prevent a European Union-approved product from being marketed in

the U.S. would be for FDA to prove that it is unsafe or ineffective. Essentially, this would take us back to the type of drug regulation that existed in this country prior to 1938, with the commensurate significant loss in consumer protection.

It should be noted that although this provision would tie the FDA's hands regarding drug and device approvals, it would not require the same allegiance to foreign government actions for a decision to withdraw marketing approval or not to approve the product in the first place. Under S. 1477, if the European Union or United Kingdom withdraws a drug from the market, it would not automatically be withdrawn in the U.S. Moreover, this provision could provide foreign owned companies, particularly those that are government subsidized, a dangerous competitive tool in the world market.

The bill's requirement for third party reviews is equally troubling. The third party review sanction set forth in Section 743 raises particular concerns, in addition to those generally applicable to the feasibility of third party review. Once the provision is triggered, it would interrupt consideration in the middle of the overall process for many applications. Companies would be faced with having reviews performed by a third party

reviewer who has very little knowledge of the specific development process for the drug and/or of the agreements made during that process. The contracting requirement assumes that well trained staff, free of conflicts of interest yet familiar with the regulatory review process will be readily available to perform this work. We doubt whether that would be, in fact, the case.

The feasibility of third party review raises important questions that should be, and are being, carefully examined. FDA's scientists and experts are charged with exercising independent and unbiased judgement. They comply with stringent financial disclosure and conflict of interest requirements designed to protect the decision-making process against bias. It is not clear whether, and how, this independence can be maintained with private sector review organizations. The Agency has initiated two different pilot projects to assess the feasibility of such a program.

The substitution of judgment also extends to the manufacturing area. When a contractor has given a manufacturer good marks for its production processes, FDA is prohibited from inspecting the

plant for two years unless the Agency learns through other means that there is something seriously wrong at the plant.

The bill also undermines consumer protection through other default mechanisms. Now, if FDA suspends or revokes the license of a blood bank because it has created a public health danger, it is shipping HIV-contaminated blood, it cannot resume shipments until it has fixed its manufacturing problems. Under S. 1477, a blood bank that has had its license suspended or revoked can resume shipping blood even before it has fixed its manufacturing problems, if the FDA misses the 30 day reinspection deadline by even one day. (Section 606)

Similarly, the changes the bill proposes for review of indirect food additives could result in unsafe food additives being sold if FDA does not fully review an indirect food additive notification and publish its decision on that food additive in the Federal Register within 90 days. (Section 902) The 90 days is an unrealistically short deadline; it would take many FTEs not provided for in this bill, to lower review times to 90 days. Therefore, FDA either will be forced into premature disapprovals, or it will have to watch as the public is exposed to industrial

chemicals which pose a potentially serious risk to the public health.

Expanding Access To Unapproved Therapies

The provisions for treatment access to investigational products are clearly intended to meet real patient needs. But as drafted they go too far. We, too, want patients who have no good treatment options to have access to the newest therapies, even before they have been fully studied and evaluated. We have made experimental drugs available early-on in the process by our use of treatment INDs, parallel track, single patient protocols, and emergency use INDs. But we do it in a way that still permits the basic research on the drug to be done, so that eventually physicians and patients know whether the promising therapy really works, and how best to use it.

Unfortunately, S. 1477 (Section 202) would permit drug and device companies to side-step completely FDA's approval process and go into the manufacture, promotion, and sales of a product for any serious disease or condition without FDA approval. Under S. 1477's provisions, expanded access protocols could be given for any product that diagnoses, monitors, or treats a serious

disease or condition, so long as other therapy is not "comparable or satisfactory."

In addition, S. 1477 would permit the manufacturer to widely promote the availability of the expanded-access protocol. (Section 202) Unlike FDA's current system for cost recovery under a treatment IND, there is no requirement in the bill that adequate enrollment be obtained for clinical trials that are designed to determine the safety and effectiveness of the product, and that the manufacturer pursue marketing approval with due diligence. In short, the patient would have to pay full price for an experimental product, and the company would be under no obligation to ever find out its true value. Coupled with the provisions for cost recovery, promotion of the availability of experimental treatments would create a climate where the unscrupulous could sell untested hope with scant risk of being found out and only weak sanctions if they were. The 1995 Health and Human Services Inspector General's review of commercialization of unapproved medical devices shows this is not just a theoretical risk but a predatory business practice hard to control even with today's stronger law.

Advisory Committees And Scientific Review Groups

We agree that advisory committees are an important part of FDA's review processes. We value the guidance and direction we receive from these outside experts. But S. 1477 would create "scientific review groups" that would be expensive, difficult to handle administratively, and would meet so often that we doubt that respected experts would be willing to serve on them. (Section 106)

Perhaps more importantly, the scope of the scientific review groups set up by S. 1477 is so expansive they would have the ability to second-guess any significant scientific decision made by FDA, to an extent that the scientific review groups would become a shadow FDA. Now, advisory committees usually meet three to four times a year; this bill would require that they meet at a minimum six times a year (Section 106), at an increased cost to the Agency of approximately $6,000,000. The costs in fact would be higher, because advisory committees would have to meet much more often in order to hear appeals on every significant decision made by FDA on whether a clinical trial should start, how a protocol should be designed, or whether an application should be accepted for review by the Agency (Section 107). The bill also

places other unreasonable demands on both FDA and the review committee members, in that it would triple the time before which meetings must be announced and agendas set, and permits committee members to be inundated with paper and lobbied by companies and other individuals. In short, scientific review committees would impede drug review, not enhance it.

We also think that there must be appropriate methods for appealing decisions made by first-line reviewers, when a company disagrees with such a decision. Those mechanisms exist, and last June I asked the Center directors to review the existing appeal mechanisms, make improvements where possible, and insure that companies are aware of the availability of such mechanisms. There already have been significant changes in how appeals from clinical holds are handled, and the Centers are working hard to train their staffs so fewer decisions need to be appealed. But taking every disagreement to a scientific panel during the entire drug development phase will inhibit, rather than enhance, communication between industry and FDA, creating an adversarial process in place of a cooperative one, and ultimately increasing overall drug review times.

appeals

Limiting Agency Flexibilitly in Review Process

There are a number of provisions in S. 1477 that would dramatically limit the Agency's ability to manage its resources efficiently. These provisions would adversely affect both the product review process and the other public health activities of the Agency. For example the bill orders the Agency to consider certain products (such as radiopharmaceutical drugs) in particular divisions (Section 402); it forces us to keep biologic product licenses, even when we are willing to eliminate them for some types of biologics (Section 606); conversely, it eliminates establishment licenses, even for products that could be most simply and effectively regulated using ELAs. (Section 606) ELA reviews have found examples of cross-contamination and seriously violative air handling systems. In addition, certain technologies may actually be more flexibly regulated by the use of the ELA, for example, cellular and gene therapies, and xenotransplantation products (tissues and organs transplanted from animals to humans). GMPs alone would not be adequate to assure that proper controls are maintained to prevent the spread of infectious diseases.

It should be beyond dispute today that you cannot legislate good management. We need to have clear performance goals and we need to be held accountable for meeting those goals. But we need the flexibility to change in response to changing conditions, reallocate resources to address the most significant public health problems, to respond to emerging issues. Good management comes first and foremost from good managers. I believe we have such managers, and that they should be allowed to do their jobs.

There also are sections of S. 1477 that express laudable goals, but again are so expensive as to be totally unrealistic in this budgetary climate. Information systems (Section 104), the formal publication and compilation of all policy statements (Section 105(B)), the extensive meetings on clinical trial design, and the additional advisory committee meetings would cost more than FDA could conceivably afford to spend in these areas.

Similarly, the time frames specified for a variety of actions, such as reinspections and issuance of regulations are unrealistically short.

CONCLUSION

I hope the concerns I am expressing about this bill will not be construed as commitment to the status quo. The Agency looks forward to continuing to work with the Committee and others on new ideas on how we assess new product effectiveness, how we get products labeled to reflect the best data on their use, how we get clinical development, and how we get the Agency's independent review of new products to go faster so scientific advances move to the bedside more quickly. (I agree that we need to consider alternative ways to determine whether new uses for existing products are sufficiently scientifically credible to be included in a product's labeling.) We also recognize that some claims for diagnostic products or surgical tools are supported by different kinds of data from those we generally expect for other kinds of products. We need to describe clearly when this is the case.

There are provisions of this bill that reflect good ideas. As I stated at the beginning, we believe that there is still a great deal that we can do to improve our ability to get safe and effective products to patients as soon as possible. We have a strong foundation in the Prescription Drug User Fee Program, the efforts that have been made under the Administration's

reinventing government initiative, and our successes in expediting development and approval of AIDS drugs, on which to build. The Agency and industry have demonstrated that by working together we can develop reasonable solutions to regulatory problems solutions that serve and promote the public health. We look forward to working with the Committee and the industry on finding even more ways to improve the existing system.

ATTACHMENT 1

Toxicology

Experts: toxicologists, pharmacologists

Questions Considered:

Could the drug cause rare, severe or irreversible side effects?

Has the toxicity of the excipient been tested? Are we sure they are safe to use in people?

Can the drug cause cancer?

Does the drug cause birth defects in animals?

What are the appropriate doses to test in humans and what toxicities should be screened?

Chemistry Review

Bulk drug--usually made outside USA

Questions Considered:

Are the raw materials tested to make sure they are what they are supposed to be?

What chemicals are used/occur when making the drug? How much of them are in the final product? Are they checked for? Are they toxic, carcinogenic?

How carefully is the final product tested? Will they know if something goes wrong?

Are there other drugs in the product?

Final product
General
For Pills:

Will the pills crumble as they are stored?

If light shines on the pills, will they deteriorate?

Will the strength of each pill be roughly the same, time after time?

Are there other things in the pills that could be harmful?

Has their toxic potential been tested?

Have the excipient (other ingredients) ever been used in people before? Are they safe?

FDA will test samples of the product: do the manufacturer's tests actually work in an independent, experienced lab's hand's?

For injectables:

Are they sterile? do they contain particles that could get stuck in the lungs?

Do the tests on the product really work?

Will chemicals in the container get into the product?

Will the stopper keep germs from getting into the vial?

Will the stopper crumble after contact with the drug?

Biopharmaceutics

Experts: Clinical pharmacologists, pharmacologists, biopharmaceutics experts, pharmacokineticists

Questions Considered:

Will the drug that's sold deliver the same amount of drug as the drug used in the clinical trials? Will it have different effects?

How much drug gets into the blood after taking a pill? How long does it stay in the blood? How does it leave the blood? The kidney, the liver?

What if a person has liver disease? Will the drug be more toxic? Will it build up in the blood? What about people with kidney disease?

What if person is taking other drugs? How will they interact with this drug? Could this drug cause dangerous or fatal side effects by interactions with other drugs?

Can the drug be taken with food?

Will the drug build up in the system if taken repeatedly? Does the body change how it handles the drug after taking the drug for a while?

Clinical

Experts: Clinical pharmacologists, FDA inspectors, medical subspecialists (infectious disease, cancer treatments, AIDS experts, anesthesiologists, etc.), Biostatisticians, clinical trialists

Questions Considered:

Can pregnant or nursing women take the drug safely?

If someone takes the drug, is there a chance of it helping them? What are the chances? How does this compare to the risk of having a bad side effect? Is the benefit hypothetical (surrogate endpoint) or were the patients in the trials actually helped?

How many trials showed that the drug worked? How many showed that it didn't work? How could this be? Was the trial it didn't work in a fluke? or was the trial it did work in?

Were the trials done correctly? Were the trials actually conducted, were the patients actually enrolled (dry-lab of results or patients has actually occurred) Do the results actually reflect what happened to the patients (These points refer to the audit function) Did all the side effects get reported to the FDA?

Were the trials done correctly? Did the apparently favorable results occur due to drug effects or might they have resulted from chance or bias?

Will the dose be too strong for some people? Who are those people? How great is the risk to them? Should the dose be lowered in some cases?

How was the dose picked? Does it maximize benefit compared to risk?

Should children take the drug? Are there special risks for children? What about women? Are there special risks?

How many serious side effects does this drug cause? Do they cause deaths? How many deaths can be expected from use of this drug? How many other terrible side effects for example, killing all the blood cells (aplastic anemia), liver failure, kidney disease? Can this be predicted in any way? Are there people who shouldn't take the drug? Do side effects multiply if you take other drugs with this one? Which drugs? Is there an antidote to the side effect?

How many less serious side effects does the drug cause? What is the rate--one in every ten people, half the people, one percent of the people?

Manufacturing

Experts: Chemists, Manufacturing experts, Microbiologists, FDA inspectors

Plant:

Is it there? Is it usable?
Are conditions safe for making drugs?

Quality control:

After one drug is made, is the equipment leaned and checked before the next one goes through?

Do they really DO all the tests on the product?

Do they make sure the labels aren't mixed up?
Is the water safe? Is the air clean?

How often are the products out of spec?

Are chemicals stored safely--could they get mixed up?

Labelling Review

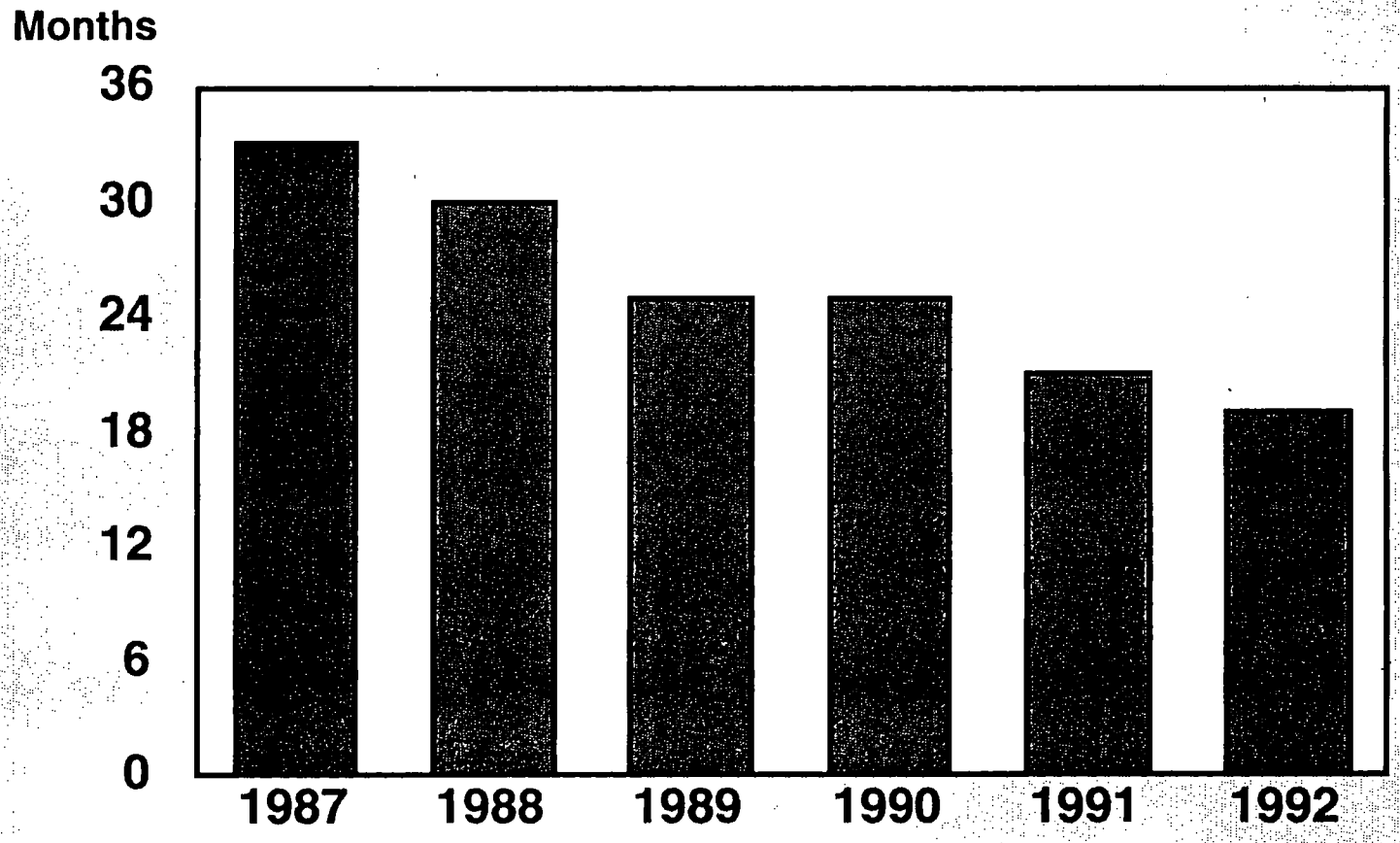
Experts: Regulatory experts, pharmacists, clinicians, clinical pharmacologists, chemists, biopharmaceutics experts, lawyers.

Questions Considered:

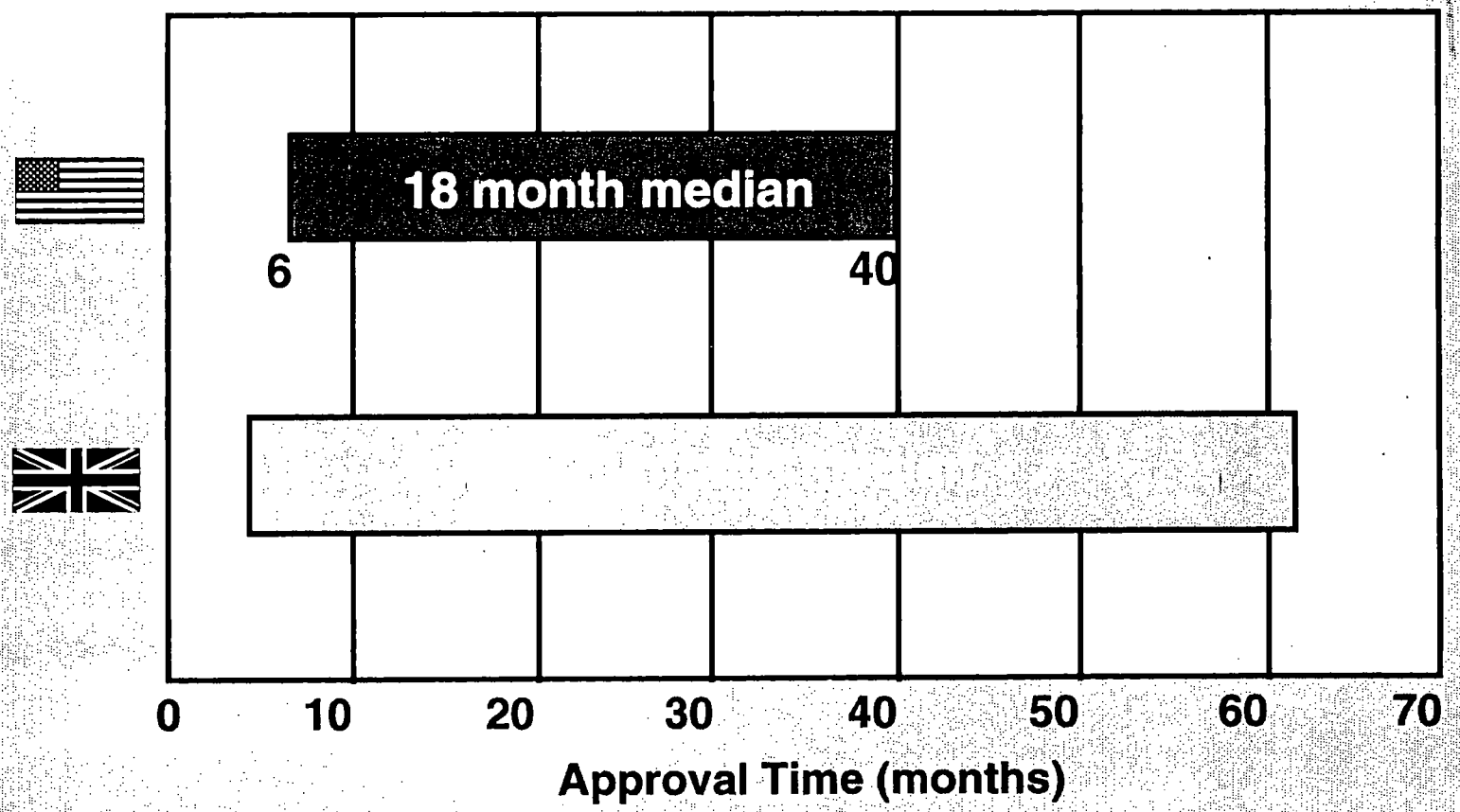
Does the label clearly reflect the above findings, to truthfully relay all information about the drug?

General Accounting Office Analysis of Average Drug Approval Time

1987- 1992



GAO Comparison of US/UK Approval Time - 1994



Twelve Month User Fee Goals

Applications submitted in:

FY1994	55% on time
FY1995	70% on time
FY1996	80% on time
FY1997	90% on time

Twelve Month Review*

New Drugs and Biologics

Actual 96% on time

Goal 55% on time

* If major amendment submitted late in the process, an additional three months is granted.

Antiretrovirals Currently Approved

For HIV infection & AIDS-related conditions

Product	Approval	Review Time to Approval
AZT	March 1987	3.5 months
ddI	October 1991	6 months
ddC	June 1992	8.5 months
d4t	June 1994	6 months
3TC	November 1995	4.5 months
saquinavir	December 1995	3 months

Dates of Approval

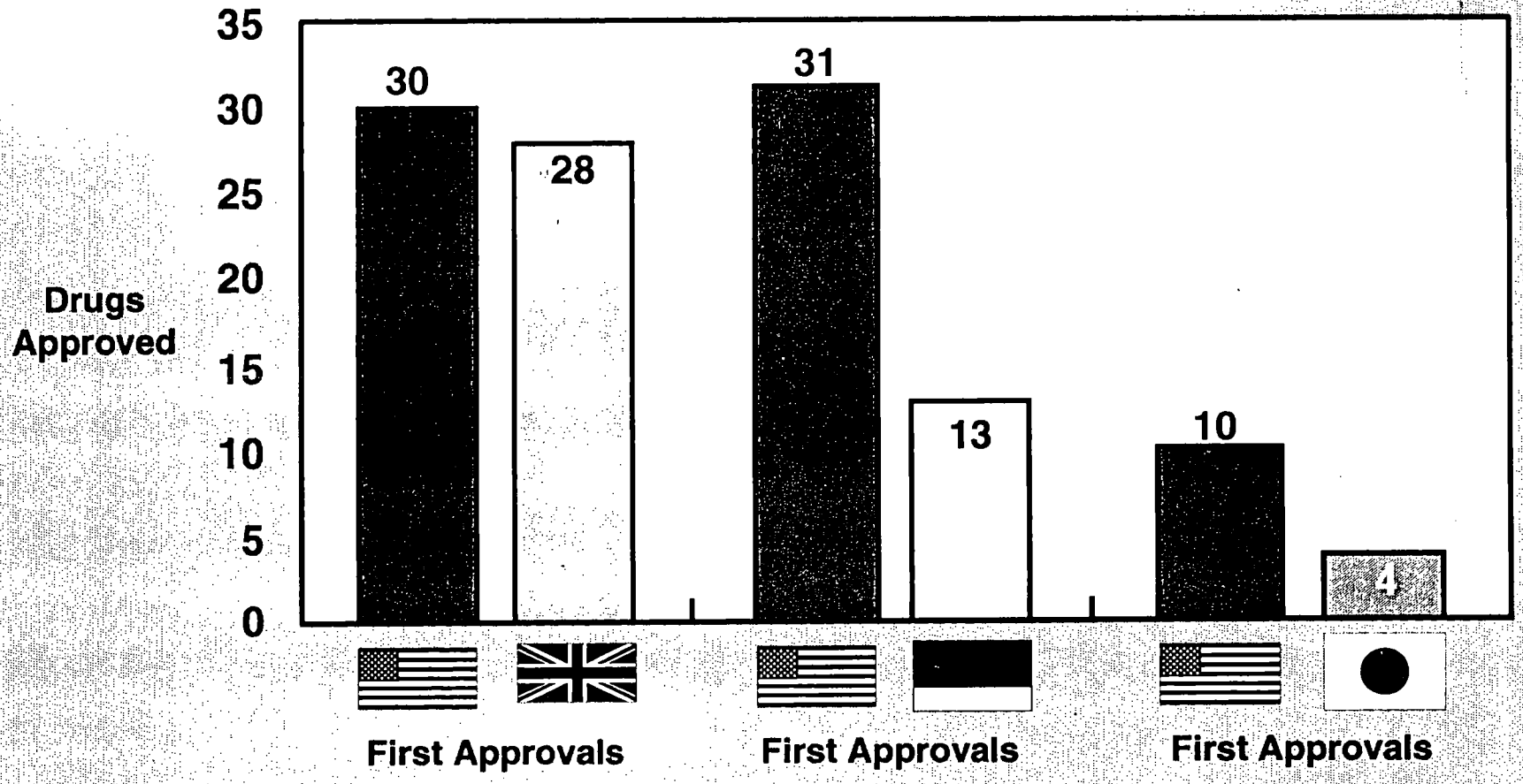
	saquinavir	3TC	d4T	ddC	ddI	AZT
	December 1995	November 1995	June 1994	June 1992	October 1991	March 1987
	Not yet approved	Not yet approved	January 1996	January 1994	May 1992	March 1987
	Not yet approved	Not yet approved	January 1996	January 1994	August 1992	April 1987
	Not yet approved	Not yet approved	January 1996	September 1994	February 1994	March 1987

Dates of Approval

	Fludarabine	Taxol	Dornase Alpha	Interferon Beta-1B	Riluzole
	April 1991	December 1992	December 1993	July 1993	December 1995
	May 1994	November 1993	March 1994	November 1995	Not yet approved
	Not yet approved	November 1993	September 1994	November 1995	Not yet approved
	November 1994	November 1993	January 1994	November 1995	Not yet approved

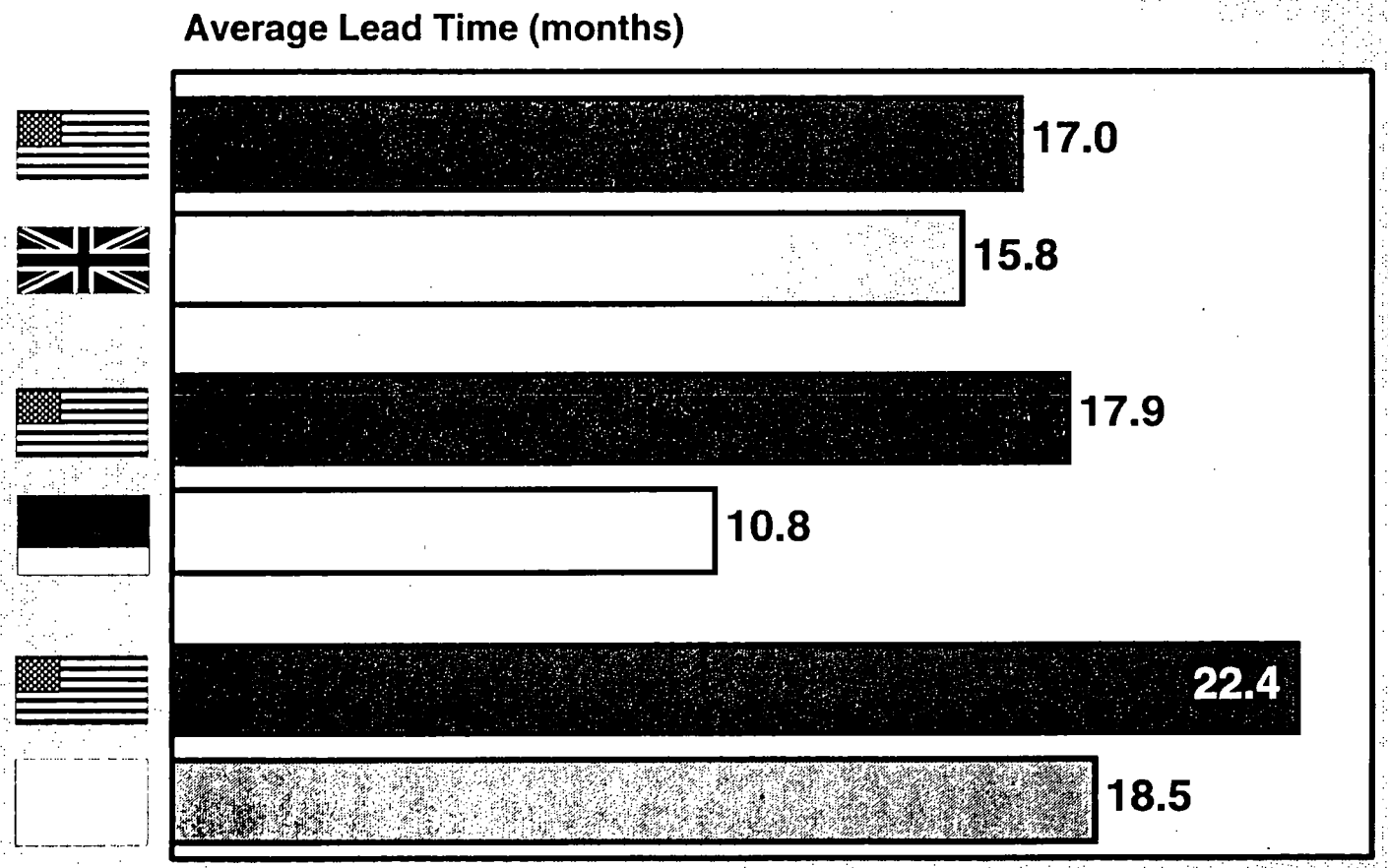
Who is first?

Drugs approved in both countries



How much faster?

Drugs approved in both countries



New Drugs Approved in US But Not in UK

- BENAZEPRIL
- CEFPROZIL
- DEZOCINE
- DOXACURIUM CHLORIDE
- *FELBAMATE - RESTRICTED IN US - 1994*
- *GALLIUM NITRATE*
- HALOBETASOL
- *HISTRELIN*
- *IMIGLUCERASE*
- INTERFERON ALFA-N3
- *INTERFERON BETA-1B*
- MASOPROCOL
- MERIEUX VARICELLA VACCINE
- *PEGADEMASE BOVINE*
- PEGASPARGASE
- *STAVUDINE (d4T)*
- *SUCCIMER*
- *TACRINE*

Priority drugs in blue

New Drugs Approved in US But Not in Germany

- CEFPROZIL
- *CLADRIBINE*
- DEZOCINE
- DOXACURIUM CHLORIDE
- *FACTOR VIII - rDNA (KOGENATE)*
- *FELBAMATE - RESTRICTED IN US - 1994*
- FLOSEQUINAN - WITHDRAWN WW 1993
- *FLUDARABINE*
- FLUOSOL - PERFLUOROCARBON
- *GALLIUM NITRATE*
- HALOBETASOL
- *HISTRELIN*
- *IMIGLUCERASE*
- INTERFERON ALFA-N3
- *INTERFERON BETA-1B*
- LODOXAMIDE
- LOSARTAN
- MASOPROCOL
- MERIEUX VARICELLA VACCINE
- *MIVACURIUM*
- *MORICIZINE*
- NEFAZODONE
- *PEGADEMASE BOVINE*
- ROCURONIUM BROMIDE
- *SALMETEROL*
- *SARGRAMOSTIM (GM-CSF)*
- SERTRALINE
- *STAVUDINE (d4T)*
- *SUCCIMER*
- *TACRINE*
- TRIMETREXATE
- VENLAFAXINE

Priority drugs in blue

New Drugs Approved in US But Not in Japan

- *ALGLUCERASE*
- *ATOVAQUONE*
- **CALCIPOTRIOL**
- **CEFPROZIL**
- *CLADRIBINE*
- *COLFOSCERIL*
- **DESFLURANE**
- **DEZOCINE**
- *DORNASE ALFA*
- **DOXACURIUM CHLORIDE**
- *EFLORNITHINE*
- *FACTOR VIII - rDNA (RECOMBINATE)*
- **FAMCICLOVIR**
- *FELBAMATE - RESTRICTED IN US - 1994*
- *FINASTERIDE*
- **FLOSEQUINAN - WITHDRAWN WW 1993**
- *FLUDARABINE*
- **FLUOSOL - PERFLUOROCARBON**
- **FLUVASTATIN**
- **FOSINOPRIL**
- *GABAPENTIN*
- *GALLIUM NITRATE*
- **HALOBETASOL**
- **HEPATITITIS A VACCINE - HAVRIX**
- *HISTRELIN*
- *IDARUBICIN*
- *IMIGLUCERASE*
- **INTERFERON ALFA-N3**
- *INTERFERON BETA-1B*
- *INTERFERON GAMMA 1B*
- *KETOROLAC - WITHDRAWN GER 6/93 & FRA 12/93*
- *LAMOTRIGINE*
- *LEVOCABASTINE*
- **LODOXAMIDE**
- **LORACARBEF**
- **LOSARTAN**
- **MASOPROCOL**
- **MERIEUX VARICELLA VACCINE**
- **MILRINONE (IV)**
- *MIVACURIUM*
- *MORICIZINE*
- **NEFAZODONE**
- *PACLITAXEL (TAXOL)*
- **PAROXETINE**
- *PEGADEMASE BOVINE*
- **PEGASPARGASE**
- *RIFABUTIN*
- *RISPERIDONE*
- **ROCURONIUM BROMIDE SALMETEROL**
- *SALMETEROL*
- *SARGRAMOSTIM (GM-CSF)*
- **SERTRALINE**
- *STAVUDINE (d4T)*
- *SUCCIMER*
- *SUMATRIPTAN*
- *TACRINE*
- **TAZOBACTAM (COMBO)**
- **TEMAFLOXACIN - WITHDRAWN WW 6/92**
- **TORASEMIDE (TORSEMIDE)**
- **TRIMETREXATE**
- **VENLAFAXINE**
- *ZALCITABINE (DDC)*

Priority drugs in blue

Reinventing FDA - Completed

- Eliminated establishment licenses for most biotech drugs
- Eliminated lot release for most biotech drugs
- Allowed use of pilot facilities for biological drug development
- Eliminated FDA review of hundreds of medical devices
- Implemented new food safety system (using performance standards)
- Eliminated FDA approval of manufacturing changes for drugs and biologics
- Eliminated medical device "Reference List"
- Published policy statement that new drugs not be proved more effective than other drugs
- Relaxed medical device export policy
- Provided exemptions from most environmental impact policy

Reinventing FDA - Under Development

- Third party review pilot program for medical devices
- Harmonized application for all drugs and biologics
- Elimination of GRAS substance reviews
- Reform of food additive petition process
- Greater use of the private sector in monitoring imported foods
- Relaxation of animal drug exports (requires statutory change)
- Elimination of medicated feed application (requires statutory change)
- Elimination of antibiotic and insulin monographs (requires statutory change)
- Automated management processes (SMART)
- Automated import entry system (OASIS)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

DAVID A. KESSLER, M.D.

COMMISSIONER OF FOOD AND DRUGS

DEPARTMENT OF HEALTH AND

HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH AND ENVIRONMENT

COMMITTEE ON COMMERCE

U.S. HOUSE OF REPRESENTATIVES

MAY 1, 1996

FOR RELEASE ONLY UPON DELIVERY

Chairman Bilirakis, and members of the Committee, I am pleased to be here today as you consider a very important public health issue -- ensuring that the Food and Drug Administration (FDA) protects the nation's safety and health. Let me say at the outset that we are committed, as I know you are, to ensuring timely access to new drugs and devices that are shown to be safe and effective. We look forward to working closely with you and your colleagues in the House and Senate on bipartisan legislation that accomplishes this goal.

INTRODUCTION

The FDA's primary mission for 90 years has been to protect and promote the public health. I know you share our view that all Americans deserve assurance that the medicines they take or medical devices they need are safe and really work, and that the foods they eat are safe. We are committed to maintaining high standards so that consumers can continue to have that confidence and assurance. But high standards alone are not enough. Timely access to safe and effective products is important to the public health as well.

To meet the goal of timely approval of safe and effective products, FDA must be open to change. This is a time of unprecedented medical challenges and medical breakthroughs. An important measure of our value as an Agency will be our ability

to keep pace with these changes. Thomas Jefferson said it best: "Our laws and institutions must [move forward] hand in hand with the progress of the human mind."

As Commissioner, the first way I have sought to effect change is to attract a new generation of leaders to the Agency. Much of the progress FDA has made over the past few years began with our five new Center Directors. The many changes they have made have moved us closer to our goal. Second, we have vigorously pursued and implemented more than thirty FDA reinventing initiatives as part of President Clinton's and Vice President Gore's National Performance Review. Among the changes we have made, are speeding new cancer drugs to patients and targeting our limited resources to higher risk medical devices while no longer requiring FDA premarket review of hundreds of categories of simple devices such as tongue depressors and urinary catheters. Finally, in addition to the many changes we have already made, the administration is committed to supporting bipartisan legislation that does not lower current standards for product safety and efficacy.

If we are to achieve our shared goals of improving the Agency's ability to protect and promote the public health by assuring the public speedy access to safe and effective products, we must base our work on FDA's current performance. Unfortunately, too many of our critics justify the call for "reform" based on how the FDA did its job in the 1980's or earlier. They have missed the

substantial progress that the dedicated doctors, nurses, engineers, chemists, microbiologists, biostatisticians, nutritionists and others at the FDA have achieved over the past several years. They would have us ignore the important lessons we have learned about the kind of change that will result in getting safe and effective drugs and devices to the market more quickly. Those who fail to recognize the Agency's performance and achievements threaten to undermine the real progress the Agency has made. While we share the goal of streamlining our operations and speeding safe, life saving drugs to the American public, undermining progress in critical public health and consumer protection is not "reform."

Let me explain what we have done.

THE FOOD AND DRUG ADMINISTRATION IN 1996

A. MEETING AND EXCEEDING THE PRESCRIPTION DRUG USER FEE PERFORMANCE GOALS

According to the General Accounting Office (GAO), the average approval time for new drug applications (NDA) submitted to the Agency in 1987 was 33 months. For NDAs submitted in 1992, the time had been reduced to 19 months. In 1995, approval times were even better: 16.5 months was the median approval time for the 82 NDAs approved in that year. For the 15 priority drugs, the

median approval time was 6 months. These latest improvements in approval times have been made possible by shortening the time for completion of most first reviews of applications to only 12 months. How did we do it? In 1992, Congress, the Agency, and the pharmaceutical industry recognized that additional resources were one key to improving FDA's review of drugs and biologicals. Congress, led by a partisan initiative of this Committee, unanimously enacted the Prescription Drug User Fee Act of 1992 (PDUFA). The Agency, in turn, committed to very aggressive application review performance standards, with higher hurdles in each succeeding year until full implementation in fiscal year 1997. These performance standards were negotiated with, and agreed to by, the pharmaceutical and biotech industries.

We already have achieved one of the major 1997 performance goals. We achieved it in fiscal year 1994 -- a full three years ahead of schedule. For the drugs submitted to FDA in fiscal year 1994, we reviewed and acted upon 96 percent of them on time. In most cases, that meant first action within 12 months.[1]

We should never forget that the ultimate goal is ensuring that American patients have access to products that work and really make a difference. By that measure as well, the FDA is delivering. The story of AIDS therapies is especially telling.

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[1] Under the provisions of the program, if a major amendment is submitted by the manufacturer late in the process, an additional three months is granted.

Of the eight antivirals used to treat AIDS, FDA was first to approve them in seven instances, DDI, DDC, D4T, 3TC, saquinivar, retinovir, and indinavir. In the case of AZT, FDA acted contemporaneously with France and the United Kingdom. On March 1, the Agency approved ritonavir, the second in a new class of AIDS drugs called protease inhibitors, and we were the first country to do so. On March 13, we approved the newest protease inhibitor, indinavar, and this was done in 42 days. But the story goes beyond AIDS. Taxol for ovarian cancer, Fludarabine for lymphocytic leukemia, Pulmozyme for cystic fibrosis, Betaseron for multiple sclerosis, Riluzole for Lou Gehrig's disease, and Cognex for Alzheimer's were all first approved in the United States.

B. FDA IS A WORLD LEADER IN DRUG APPROVAL

One measure of FDA's drug review performance is found in how we compare to the performance of other major regulatory agencies around the world. Three separate studies demonstrate that FDA compares extremely well. First, at the request of this Committee, GAO looked at how FDA was performing, even before PDUFA was enacted. It found that by 1994, FDA review and approval times were faster than those in the United Kingdom -- a country whose regulatory system many critics like to cite as a way of doing things better and faster.

Second, FDA conducted an analysis of the "new molecular entities" (NMEs) introduced throughout the world between 1990 and 1994. We looked at when those drugs were approved here and in Germany, Japan, and the United Kingdom -- four countries that account for 60 percent of global pharmaceutical sales. Let me just give you a brief glimpse at the numbers in the FDA study, "Timely Access to New Drugs in the 1990s: An International Comparison." There were 58 of these NMEs that had been approved in both the United States and the United Kingdom. We approved 30 of them first, the United Kingdom 28. There were 44 of these NMEs approved in both the United States and Germany. We approved 31 of them first, Germany 13. There were 14 of these NMEs approved in both the United States and Japan. We approved 10 of them first, Japan 4.

Moreover, it is not just the numbers that compared well. We also found that there are numerous drugs with important therapeutic values available here, but not in these other countries. On the other hand, virtually all of the drugs available in these other countries but not approved here have closely related drugs (i.e., therapeutic equivalents) in the United States. Moreover, the United States is first to approve a significant proportion of "global" drugs -- those ultimately approved by more than one country.

The third, and most recent analysis was conducted by the Centre for Medicines Research, an industry funded, not-for-profit

research group in the United Kingdom. This analysis once again demonstrated that FDA is a world leader in both the quality of its drug reviews and the timeliness of its approval. CMR found that FDA's median approval time for NMEs in calendar year 1994 and 1995 was as short as that in the United Kingdom and shorter than those in France, Spain, Germany, Australia, Japan, Italy, and Canada. Moreover, the FDA has had more first launches of worldwide NMEs than any single European country since 1990. In fact, CMR's analysis of worldwide NMEs launched in the United States and Europe showed that the United States has had a higher percentage of first launches than the top three European countries combined.

What these three studies demonstrate is that if you are an American patient, you have access to therapeutically important new drugs that have been proven safe and effective sooner than any other country's citizens.

C. MAKING NEW DRUGS AVAILABLE SOONER

In addition to shortening review times, the Agency has developed a number of innovative and well accepted mechanisms that give seriously ill and dying patients access to potentially valuable therapies outside of the clinical trials needed for drug development before they are approved for marketing. We recognize that this approach has its risks. But we also recognize that

when it comes to getting needed therapies to terminally ill patients, the riskiest thing we can do is to be unwilling to take risks.

We have instituted innovative pre-approval policies, such as the "treatment IND," under which patients for whom there is no satisfactory alternative treatment may get access to a promising drug after clinical testing shows that it may be effective, but before it is approved for marketing. Under FDA's "treatment IND" provision, treatment is given under simplified protocols that collect important safety and, where appropriate, efficacy data.

We also have developed a process to accelerate approval of drugs for serious and life-threatening diseases, by approving such drugs for marketing before the data from traditional clinical trials are complete, if the drug shows an effect on a "surrogate marker." A surrogate marker is a laboratory measurement, such as an increase in the number of CD4 cells in a person with HIV, that is thought to predict actual clinical outcome, such as longer life or a decrease in infections. Recently, we announced a new initiative for cancer drugs that incorporates accelerated approval using tumor shrinkage as the surrogate marker.

"Accelerated approval" is a kind of "conditional approval," because the applicant must agree to conduct further studies after marketing to measure the actual clinical outcome, not just the

surrogate marker. If the studies do not verify a clinical benefit, FDA can revoke the approval. We have already approved ten drugs under this accelerated approval process since it was put in place in December 1992. They include six drugs to treat AIDs and AIDs related illnesses, three drugs to treat cancer, and one drug to treat multiple sclerosis.

Finally, we 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 have received access to promising new drugs while they were being studied.

D. IMPROVING MEDICAL DEVICE REVIEW TIMES

We also are making significant strides in strengthening our medical device program. Improvements have been made in the times for the review and approval of medical devices. With respect to the so-called 510(k) process, through which 98 percent of all medical devices evaluated by FDA reach the market, the average review time in fiscal year 1995 was 138 days, down 24 percent from the 182-day average in fiscal year 1994. Moreover, backlogs have been virtually eliminated. Only nine 510(k)s were overdue at the end of FY 95, compared to 500 a year ago and nearly 2000 in December, 1993. The average review time for those devices

needing premarket applications (PMAs), which in fiscal year 1995 was 20 months, is still too long, but we are making progress there as well.

It is important to remember, however, where the Agency was in the 1980's. Congress found -- as did the Agency -- that the standards for the review of clinical data on how to use medical devices were lacking. FDA looked at devices the way an engineer would; we did not focus sufficient attention on whether the device would actually make the patient better. Congress told us to do better, and we have. The clinical standards for medical device reviews have been bolstered significantly, and now we are hard at work on reducing review times even further.

E. IMPROVING ANIMAL DRUG AND FOOD ADDITIVE REVIEW TIMES

The American food supply is one of the safest in the world. The premarket determinations that animal drugs are safe and effective, especially when they are intended for use in food producing animals, and that food additives and color additives are safe constitute critical links in the food safety chain.

As is the case with human drugs and devices, the Agency has recognized the need to improve the timeliness of the product review processes in both these areas. In the new animal drug area, approval times that had steadily increased between 1988 and

1994 have begun to decline. This is particularly significant given the changing nature of the types of applications being submitted to the Agency. Five years ago, a large number of the applications were for combination feed drugs, which consist of two or more drugs each already approved for specific indications and species. Today, more applications are for new chemical entities, new species, or new indications. As a result, the complexity of the review has increased considerably. The Center for Veterinary Medicine (CVM) has developed procedures to facilitate the development of better applications and to expedite the review process. By meeting with sponsors prior to the submission of their investigational new animal drug exemption applications and encouraging the phased submission of the technical sections of the New Animal Drug Application, CVM has reengineered the review process to decrease approval times and increase the availability of safe and effective animal drugs.

Similarly, the Center for Food Safety and Applied Nutrition (CFSAN) has developed a plan to increase the timeliness and predictability of Agency action on food and color additive petitions. First, in order to address the backlog of pending petitions, the Agency has allocated additional resources to the program: 23 Agency scientists have been reassigned temporarily to the food additive program; the Agency is awarding contracts for expert review of certain portions of food additive data packages; and one and one-half million dollars was spent for enhanced

computing facilities. With these efforts, we have already begun to see a decrease in the petition inventory.

Second, we instituted a threshold of regulation policy under which noncarcinogenic indirect food additives that do not present any substantial safety concerns are exempted from the petition process. The Agency processed 47 submissions under this new policy in 1995.

Finally, we again recognize that one way to decrease review times is to improve the quality of the food additive petitions filed with the Agency. We have been working with the industry to do that. FDA personnel have begun conducting workshops for petitioners to discuss what data and studies are needed for a complete food additive petition.

REGULATORY INITIATIVES AND MANAGEMENT REFORMS

Mr. Chairman, we have improved review times without sacrificing the high standards that give Americans confidence that their drugs are safe and work. Under PDUFA, the Agency was assured of adequate resources to do the job and the job was clearly defined through performance goals. At the same time, how to achieve those goals was left to Agency management, and accountability to Congress was assured through the five year authorization. That was real reform. Reauthorization of this program should be a

cornerstone on which we build other improvements.

The progress we have made is the result of much more than the additional resources available under PDUFA and extends beyond the drug review process. Of equal significance has been the commitment of Agency management to streamline and improve the way we regulate. I think we all can agree that strong consistent management, the removal of unnecessary regulatory burdens, and the elimination of wasteful or inefficient practices all serve the critical public health goals to which we are committed. The Agency's contribution to the Administration's Reinventing Government Initiative well demonstrates the depth of our commitment to improving our regulatory processes.

FDA's initiatives, which will speed the availability of new products, streamline FDA procedures, and reduce regulatory burden without sacrificing safety, touch all of the regulated product areas. In biologics, for example, we have eliminated the establishment license application (ELA) and individual lot release requirements for well characterized therapeutic biotech drugs. According to the biotechnology industry, these changes will save their companies millions of dollars, reduce required paperwork by thousands of pages, and cut drug development time by months. In drugs and biologics, we have reduced and are working to continue to reduce the number of manufacturing changes that require pre-approval and have proposed regulations to reduce the

number of environmental assessments required to be submitted by industry.

In the device area, not only have we exempted 572 categories of low-risk medical devices from premarket review, we also recently began implementing a pilot program for the third party review of certain low risk medical devices in classes I and II.

In the area of food safety, FDA is working with the industry to build safety controls into their food production system. The Hazard Analysis Critical Control Points System (HACCP), towards which the Agency is moving, is designed to replace the old system of detecting and correcting problems after they occur with a system of preventing them in the first place. It permits companies to devise and implement food safety plans uniquely suited to their needs.

Finally, in the area of animal drugs, we are seeking to replace the current system of requiring submission of medicated feed applications for individual feeds with a system to license facilities that comply with GMPs.

I do not have time today to adequately list or describe all of our initiatives, so I am attaching an appendix to my testimony that sets forth summaries of our efforts and accomplishments. Collectively, these efforts reflect the Administration's

commitment to reinventing government while preserving the important health and safety protections that the American people rightly expect for these products.

THE HOUSE REFORM BILLS

Mr. Chairman, I would like to address the three reform bills that are the subject of today's hearing. We understand, from conversations with the majority, that there likely will be some changes to the three bills and we look forward to working with members of the Committee to improve these bills. However, my testimony today is based on the bills as they were introduced and as they stand before the Committee today.

Rather than address each bill and provision separately, I will address the concepts or provisions about which the Agency has the most serious concerns.

First, I will address a concept common to all three bills, and one that the Agency finds to be extremely troublesome -- the privatization of FDA's review functions.

Second, I will discuss a number of other provisions that we believe would result in unsafe products being sold to the American public.

Third, I will address the provisions that are problematic because they actually lower current efficacy standards.

Fourth, I will discuss the provisions in the food bill that undermine the Nutrition Labeling and Education Act of 1990, one of Congress's most popular public health measures in the last decade.

Finally, I will touch briefly on the bureaucratic requirements these bills impose, which will make it harder, not easier, for FDA to meet its goal of quickly getting quality products on to the market.

A. ALL THREE BILLS WOULD GIVE PRIVATE PARTIES THE RESPONSIBILITY FOR REVIEW FUNCTIONS THAT DIRECTLY AFFECT THE PUBLIC HEALTH

All three bills include privatization of FDA's review functions. Specifically they would permit third parties to make approval decisions for new drugs, devices, food and color additives, and health claims for foods. The bills would allow the review of these products and claims by reviewers who are paid by the industry to perform the reviews. In some instances, FDA would have a short, not very meaningful, opportunity to review the decision of the third party before that decision becomes final.

However, when a third party decided to initially classify a device into class II, which is the class into which 80-90% of all non-exempt devices fall, FDA would have no opportunity to review the decision; it would automatically become final, even if the third party incorrectly classified a high risk device as class II.

The concept of privatization of product application reviews is problematic for a number of reasons. First, FDA's scientific and clinical experts are charged with exercising independent and unbiased judgment. They comply with stringent financial disclosure and conflict-of-interest requirements designed to protect the decision-making process against bias. It is not clear how or whether this independence can be maintained with the private sector, particularly since the sponsor gets to choose and pay the private party and repeat business may depend on the sponsor's satisfaction with the private party's decision.

Second, FDA's reviewers have extensive knowledge about all of the similar products that are made by different companies around the country. When a reviewer looks at all of the drugs for arthritis and other inflammatory diseases, or all of the heart valves, what that reviewer learns from each review increases his/her understanding of that group of drugs or devices and their effect on the body. As a result, FDA reviewers see problems that reviewers with less information might not see.

This expertise was brought to bear five years ago when the Defense Department (DOD) was getting ready to do battle against Sadam Hussein. To protect our troops from possible chemical warfare, the DOD worked with a manufacturer to come up with a cream that could protect our soldiers' skin from chemical attack. DOD asked FDA to look at the data developed by the company. Our reviewer, who had looked at many other similar products, thought that some of the methodology to test the product was oddly out of line as compared to other topical skin protectants, and so he asked our investigators to verify the firm's claims. As it turned out, the consultant hired to develop test methods for the firm submitted fraudulent information and the data did not support the use of the cream against chemical attack. The DOD did not use the cream, and the consultant was prosecuted. You are not likely to find in the private sector the kind of expertise and breadth of knowledge that allowed FDA to uncover the problems with the multishield cream.

The third problem with privatization is the lack of continuity. For example, FDA's reviewers are able to work with the same drug over time -- first reviewing the IND, then reviewing the NDA. By staying involved in a drug's development, reviewers can build on what they already know. Third party reviewers may have little knowledge of the specific development process for the product and/or of the development agreements made during the process.

Mr. Chairman, we believe that contracting out product review to third parties should be done only if there is evidence that it can be done safely. A pilot is essential to determine if that can be done. This is why FDA is conducting its pilot program for low risk medical devices. We are trying to determine whether third parties can accomplish the goal of getting safe and effective products to the American public.

The privatization provisions in the bills raise additional concerns. For example, some seem to be applying different -- arguably lower -- standards for the products being reviewed. For example, the drug provision indicates that third party reviews shall be conducted under the standards and requirements of the Act, but also states that the approval standard for third party reviews is a "reasonable assurance" of safety and effectiveness, apparently an intention to lower the standard from the one currently in the FDC Act. For food additives being reviewed by a third party, the standard has been changed (arguably lowered) from "safe" meaning a "reasonable certainty of no harm," to a "reasonable assurance" that the food additive may be safely used.

Moreover, under the privatization provisions, FDA is faced with a nearly impossible burden if it disagrees with a third party that a product should be approved. For example, the drug and device provisions state that when a third party recommends approval, the application is deemed approved unless FDA finds that there is a

reasonable probability that the drug or device is not safe or effective. Under the food and color additive provisions, FDA can only deny approval of a food or color additive recommended by a third party if the Agency can demonstrate that there is a "reasonable probability" that the additive is "not safe."

Historically, it has been the responsibility of the drug, device, and additive manufacturers -- those who would profit from the products' uses -- to demonstrate to the Agency that the products they propose to market are in fact safe and, where appropriate, effective. In the case of drugs and devices, FDA's responsibility has been to review the evidence and either approve the drug or device if the Agency concurs that the product has been shown to be safe and effective, or refuse to approve the product if, in the Agency's opinion, safety or effectiveness has not been demonstrated. In the case of food and color additives, FDA's responsibility has been to review the evidence and either approve the additive if the Agency concurs that the product has been shown to be safe or refuse to approve the additive if, in the Agency's opinion, safety has not been demonstrated.

To require the Agency to demonstrate that a product is not safe or, where appropriate, not effective, is to require FDA to demonstrate something for which there may be no data because sufficient studies have not been conducted. Because more often than not there is a lack of evidence of safety or effectiveness,

(rather than definitive evidence showing that a product is unsafe or ineffective), this will be an extremely difficult burden for the Agency to meet. The effect of this shift in the burden of proof is to virtually remove FDA from the evaluation of any product that a manufacturer chooses to have reviewed by a private party. Since many of these products literally involve life and death and since there are at best very serious doubts about whether these private organizations can do an adequate job, this provision will seriously jeopardize the public health.

Finally, because there is a risk that only third parties that err on the side of approving applications and petitions will succeed in this market, there is a risk that the incentive will be for third parties to approve applications and petitions -- not to critically review them. If what this bill is trying to accomplish is getting safe and effective products on to the market, broad privatization will not accomplish that end.

B. ALL THREE BILLS WOULD INCREASE THE POSSIBILITY OF UNSAFE/INEFFECTIVE PRODUCTS REACHING THE MARKET

Many of the provisions in the House bills weaken the standards under which FDA has operated. Obviously, we have serious concerns about the provisions that would change the basic efficacy standards, and I plan to spend some time discussing

those provisions. But first, I would like to discuss the other measures in these bills that would undermine the Agency's ability to protect the American public from unsafe products. These provisions undercut safety either because they exempt certain activities or products from FDA review or oversight or because they limit the type of information that FDA can ask for or review. Although there is some overlap, I will address the bills separately.

1. H.R. 3199 -- Drugs and Biologics

Removal of Protections for Subjects of Drug Testing. As you know, FDA plays an important role in overseeing the safety of drug experimentation in humans. H.R. 3199, however, eliminates much of our ability to protect human subjects.

For example, the bill shortens the amount of time FDA has to review an investigational new drug application (IND) before clinical trials can begin. It also cuts back on the amount of information FDA can receive when it is evaluating whether to allow an investigational new drug to be administered to human subjects for the first time. The shortened timeframe and the limited information together make it difficult for FDA to stop a potentially dangerous trial. In addition, Phase I and Phase II studies (which are the earliest stages of drug testing in humans) could be conducted without any FDA review of the investigation.

Finally, the bill limits FDA's ability to stop a clinical trial. In fact, the bill would permit trials to continue even though the investigators are not qualified or the sponsor has submitted inaccurate information to the investigator. The effect of the bill is to eliminate important protections that now exist for these investigational studies.

Summary Data. After a sponsor of a new drug has completed its studies, it compiles a new drug application (NDA), which includes a report summarizing the results of the study. In addition to that report, the sponsor will have primary data, which consist of data tabulations (listing of the data points) and case reports (i.e., the forms on which the investigators have listed their observations).

Under current law, when FDA reviews an NDA, it receives the summary report and the data tabulations for all study subjects. FDA initially receives the actual case reports only for subjects who have died or dropped out of the study, unless the Agency asks for additional case report forms.

Section 4 of H.R. 3199 would permit sponsors to submit summary data -- i.e., the study report -- and only those data tabulations and case reports relating to deaths or drop outs due to adverse reactions. If FDA wants to see the additional data tabulations or case report forms, the office director must make a request in

writing and must specify the reasons for the request for a particular application.

This provision will seriously compromise FDA's review process. The submission of primary data is important for a number of reasons. First, it is essential to discovering and discouraging the submission of fraudulent data. Second, summary reports sometimes contain errors that can be discovered only by reviewing primary data. Third, summary data have been screened, processed, and interpreted by the sponsors, who often just do not see the shortcomings of their drugs. Someone who does not have an economic interest in the outcome of the study should be taking a hard look at the underlying data to verify the interpretation of summary data.

Finally, problems associated with a drug may be visible through an examination of the primary data that are not visible from a summary. For example, the sponsor may attribute deaths and discontinuations of study subjects to causes other than the drug, but review of the raw data may show that those adverse reactions are associated with the drug itself. Under the bill, if the sponsor does not think that the drug caused a death or drop out, the sponsor simply would not submit the data tabulations or case report forms.

Even hints of information found in patient report forms can

reveal or lead to critical information. For example, when a reviewer in the Center for Drug Evaluation and Research reviewed the patient data for dilevalol, a drug used to treat high blood pressure, she (not the company) noticed that three of the subjects suffered from liver injury while on the experimental drug. Based on her knowledge of this class of drugs, and the fact that other drugs of this type rarely caused this type of side effect, she decided to look further. The company then examined recent data available from Japan and Portugal, where the drug had already been approved. The company found severe liver injury as well as deaths. Based on this careful observation by an FDA reviewer, the drug was not approved in the United States, and it was removed from the market worldwide.

Mr. Chairman, I frankly cannot think of what the objections to submission of primary data might be. The sponsors already have the data. Given the fact that this data may now be submitted on computer disks rather than in hard copy, the "truckloads of paper" argument does not hold. If FDA's drug review times did not meet or exceed the Prescription Drug Use Fee Act goals, which the Agency and the drug industry jointly established, the argument against primary raw data might be that it delays FDA's review. However, FDA is meeting the PDUFA goals. The only possible reason that sponsors can have for not wanting to submit primary data is that they do not want FDA to scrutinize their data. The testing of drugs that we make available to the

American public should undergo this type of scrutiny.

Limiting Consideration of Certain Effectiveness Data. H.R. 3199 also limits what FDA can look at in making a determination of effectiveness. For example, Section 5 provides that the determination of effectiveness cannot include the evaluation of relative effectiveness unless the effectiveness of the drug is explicitly compared in the labeling to that of another drug.

Although FDA generally does not base its approval decisions on whether one product works as well as another, there are circumstances where such considerations are important. For illnesses with significant public health implications, such as those that are serious or life-threatening or that involve public health transmittal risks (e.g., sexually transmitted diseases) it generally would be unconscionable to allow marketing of drugs that are less effective than existing therapies.

For example, FDA requires a 95 percent efficacy rate for gonococcal eradication for products intended to treat gonorrhea. This is an efficacy rate products can meet today. Similarly, FDA refused to approve an HIV test kit that demonstrated a lower accuracy rate than one already on the market. It generally would not be in the public interest to have products available that are less effective in treating a public health epidemic or serious or life threatening disease.

Section 5 also provides that the determination of effectiveness cannot include the evaluation of any use not explicitly included in the labeling. This appears to prohibit FDA from requiring, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

Manufacturing Changes. As you know, FDA's ability to keep our nation's drug supply safe does not end with approval of a new drug. FDA is vigilant to make sure that the subsequent manufacturing of those approved drugs will not adversely affect their safety or effectiveness. Manufacturing changes that are made with the best intentions sometimes result in making a drug more dangerous or less effective. Because of the devastating impact manufacturing changes can have, we have made certain that companies tell us about the changes they are making and we ask that some changes come in for FDA review and approval before they are made. H.R. 3199 would permit drug and device manufacturers to make many risky manufacturing changes without first coming to FDA.

Specifically, section 13 of the drug bill would permit manufacturers of drugs, most biologics, blood, and blood components to make many changes in manufacturing without prior approval as long as there is not a resulting change in formulation or release specifications, the changes are validated, and FDA is notified in an annual report. Other manufacturing

changes would require validation, end-product testing (to determine equivalence), and notification to FDA at the time of the change (although not necessarily before a product manufactured under the changed conditions is in distribution).

The concern we have with the approach for drugs, most biologics, blood, and blood components is that even changes that do not affect formulations or release specifications can still change the safety and effectiveness of a product. Similarly, equivalence testing may not always detect problems that can affect safety and efficacy. Moreover, such products may be in distribution before FDA has had time to react to the change.

Perhaps, our concerns are best illustrated by the infamous "Cutter" incident with Salk polio vaccine. Salk polio vaccine is a "killed" vaccine -- i.e., it is free from any live virus. In the 1950's Cutter made a seemingly minor change in the manufacturing process -- it simply changed the type of filtration process used in the manufacture of the vaccine. That change let live virus into the vaccine. None of Cutter's end-product testing was able to detect the deadly change. Eleven people (including children) contracted polio and died, and about two hundred more got polio before the vaccine could be pulled from the market.

Another example relates to a change in the method of growing the

cells from which a biotechnology heart drug was made. The new method caused a change in the fine structure of the drug molecule. This change was not detected by final product testing, but it resulted in a less effective dose. Similarly, without submitting the change to FDA for review, a firm changed the particle size of bulk carbamazepine, a seizure medication. Although the product met existing specifications, the change in particle size caused the drug to absorb moisture, and thus, to dissolve more slowly than did the product made from the approved source. The slower dissolution may have resulted in patients absorbing the drug more slowly and thus, getting smaller doses. FDA received reports of seizures in persons taking the drug made from the changed bulk drug.

Similarly, under these new bills, a manufacturer could change the method of viral inactivation in a blood product used to treat hemophilia without first coming to FDA. A change to a new method that was incapable of such inactivation could result in a product that transmits hepatitis or HIV. Because FDA would not learn about the manufacturing changes until the public actually is receiving the product, it could act only after the public has been exposed to a product capable of transmitting hepatitis or HIV.

In sum, we know that even seemingly minor manufacturing changes can make a significant difference and that the problems wrought

by those changes will not always be picked up by end product testing. The bills' provisions that change how manufacturing changes are regulated is going to permit manufacturers to make changes that will harm the public.

GMP Inspections. After a drug has been approved, FDA conducts good manufacturing practice (GMP) inspections to ensure that the company can make the drug the same every time, so that batch after batch of the drug has the same therapeutic profile. Otherwise, the public may receive drugs that do not have the effect they are supposed to have or actually could cause harm. H.R. 3199 permits those inspections to be conducted by third parties. Although FDA has been exploring the use of third party inspections, it objects to section 10 of H.R. 3199 because it essentially eliminates FDA's involvement when a third party performs the inspection.

Pursuant to section 10, a third party performing a GMP inspection generally would not submit a copy of its observations to FDA, even when GMP problems exist. Instead, the third party would oversee corrections and then when the company achieved compliance would just certify to FDA that the company is in compliance. The Agency would never even know that problems had existed. Moreover, FDA would not be able to conduct a GMP inspection for two years after the third party certification, "unless justified by good cause." This is problematic because conditions can

change: a change in ownership or internal management may change manufacturing conditions, or personnel may simply drift into bad habits. The latter is more likely to occur if companies know that FDA could not reinspect for two years. Awareness that FDA can inspect at any time reinforces vigilance.

Pharmacy Compounding. One of the most glaring examples of a provision that undermines FDA's authority to protect the public from unsafe and ineffective products is found in Section 18 of the drug bill. Section 18 exempts drugs that are compounded by pharmacists on the order of a licensed physician from the drug and device provisions of the Act, and it exempts bulk drug products or other drugs intended for use by pharmacists for compounding from all of the Act's provisions, except those that relate directly to identity, purity, or quality.

The exemption has no constraints on the volume of compounding. It is likely to encourage large-scale manufacturing under the guise of pharmacy compounding. It would allow bulk drug suppliers or drug manufacturers to circumvent the approval requirements of the Act by shipping bulk drug substances to pharmacies for reconstituting or other processing. A shadow industry of unapproved generic drugs is likely to develop.

Moreover, the exemptions would allow potentially dangerous compounding. For example, sterile drugs could be compounded

(even on a large scale) without regard to current good manufacturing practices (CGMPs) for sterile products. Improperly compounded sterile products could result in serious adverse effects, including death.

2. H.R. 3199 -- Blood, Blood Components, and Human Tissue

Blood and Blood Components. H.R. 3199 deletes blood and blood components from the definitions of "biologic" and "drug." It eliminates the Public Health Service Act provisions relating to blood and blood components and creates a new regulatory scheme for them. We are concerned, however, that the new regulatory structure could endanger the nation's blood supply.

Although the language of the bill is unclear, there appears to be more limited authority to seize and recall certain dangerous blood and blood components. Moreover, the new standard for license suspension would be more difficult to meet. The bill further provides that even revocation or suspension of a license would not prevent the use of products that have left the control of the licensee unless the public health actually had been harmed. Even an extremely high risk of death might not permit FDA to prevent the use of such products through revocation or suspension. Finally, the provision permitting third party GMP inspections would encourage the blood industry to be inspected by

the organizations, accredited by FDA, to which they themselves belong. Will the American public have confidence in the safety of the blood supply when the manufacturers can self inspect?

Human Tissue. H.R. 3199 also sets forth a separate regulatory scheme for human tissue. It appears to define human tissue as including some or all cellular and gene therapies and it provides that human tissues may not be regulated as drugs, devices, or biologics. However, cellular and gene therapies should be subject to premarket controls because they require safety and efficacy determinations and more stringent manufacturing controls.

Pursuant to H.R. 3199, FDA may regulate human tissue only if it demonstrates, in writing published in the Federal Register and after a hearing before the Commissioner, that voluntary regulation under generally accepted standards is inadequate to protect the public health with respect to any particular type of human tissue or human tissue generally.

FDA has already made the determination that regulation of human tissue is necessary. The voluntary standards in place prior to 1993 when FDA issued regulations requiring HIV and hepatitis testing for tissues did not adequately protect the public health. Imported tissue from hepatitis infected donors was being brokered to U.S. companies for use in patients. Moreover, HIV has been

transmitted to patients through HIV-infected domestic tissue. Requiring FDA to revisit the question of the adequacy of voluntary standards is simply an unjustified waste of the Agency's scarce resources.

3. H.R. 3201 -- Devices

H.R. 3201 is similar to the drug bill in that it severely undermines FDA's authority to ensure that safe and effective devices are being marketed. Like the drug bill, it does this by limiting FDA's authority to review certain devices, limiting FDA's access to information about devices, and limiting FDA's authority to ensure that devices, once approved, remain safe and effective.

Exemptions from Filing a 510(k). H.R. 3201 first undermines device safety by allowing many significantly modified devices to go on the market without any kind of review. It does this by eliminating the requirement for a manufacturer to file a premarket notification (510(k)) under certain conditions.

Section 9, for example, exempts all Class I devices from the requirement of submitting a premarket (section 510(k)) notification, which is the clearance process for most devices. FDA has already exempted 572 categories of class I devices from premarket notification. FDA had public health reasons for not

exempting all class I devices. For example, FDA needs to review tests on the technical performance of hearing aids to ensure that they function as intended. Similarly, FDA should have an opportunity to review rebreathing devices, which are used as components within certain anesthesia machines, volume ventilators, and resuscitation devices and which have been directly related to death, serious injury, and serious illness resulting from complications caused by their design, and/or performance. Finally, it is extremely important to the public health that blood warmers not go on the market without any review. After all, the administration of blood that is at the wrong temperature can be fatal. Yet, H.R. 3201 would eliminate these and other important reviews.

Section 9 also eliminates FDA's role in assuring that modifications made to a device do not adversely affect its safety and effectiveness. It does so by eliminating the requirement that a manufacturer file a 510(k) for any modification other than a major change in intended use if the modification can be shown not to adversely affect the safety and effectiveness of the device. Thus, changes to materials, power sources, control mechanisms, and manufacturing processes would be permitted and FDA would not see data. This provision creates an enormous loophole to the general requirement that devices be cleared by FDA prior to marketing.

Change and innovation are important -- over time, many of the devices we now use have improved greatly -- but companies cannot always tell when their design changes are going to have deadly consequences. The Shiley heart valves illustrate this point. The company had made an artificial valve for diseased aortic and mitral valves of the heart. Picture a metal circle -- like the ring on a key chain -- with a disc inside the ring that would open up to 60 degrees, thereby letting blood flow through the valve. Unfortunately, there were blood clotting and blood flow problems with the 60 degree heart valve.

The company thought that they could fix the blood flow and blood clotting problems by having the valve open up to 70 degrees. At the time it was reported that the 60 degree valve suffered from metal fatigue and could break, causing of catastrophic events, which often resulted in sudden death. Nonetheless, Shiley manufactured the new 70 degree valves and sold them in Europe (though not in the US, because Shiley did not have the engineering and clinical data we asked for).

Unfortunately, the company's theory that the 70 degree valve would be better proved wrong. The 70 degree valve had a failure rate that was 6 times higher than that of the 60 degree valve. Had the 70 degree valve been sold in the US market, many more people would have died. This experience shows clearly the importance of independent review for "improvements" to devices.

It is as important for class II devices that are life sustaining or otherwise critical, as it was for the Shiley heart valve.

GMP/510(k) Linkage. H.R. 3201 not only removes numerous devices from FDA review, it also fails to ensure the safety of the products for which 510(k)s actually do get filed. For example, section 9 prohibits FDA from withholding a 510(k) decision because of a failure to comply with GMPs. This removes the basic assurance that new devices will be well made and work as intended. Under section 9, even a company with known manufacturing problems directly relevant to its new device, might have to be given clearance to market its device. (A similar provision appears in the drug bill, which prevents FDA from ascertaining GMP compliance prior to approving a new drug. This prevents FDA from knowing that a drug manufacturer can reliably and consistently produce high quality drugs.)

Exemptions from PMA Requirements. H.R. 3201 also would weaken the safety standards for the most complicated category of devices -- devices that currently must obtain approval of a premarket application (PMA) prior to being marketed. For example, section 9 virtually eliminates PMA review and approval of devices for specific uses. It would allow a device originally marketed for one clinical indication to later be marketed for other indications, even high risk ones, with only the submission of an abbreviated application (510(k)) that would not document the

product's effectiveness for the new indications.

Suppose, for example, that a manufacturer of an ultrasound device, approved for the general diagnostic use of evaluating soft tissue, wants to market its device for the higher risk, specific use of diagnosing cancerous breast lumps. H.R. 3201 could prevent FDA from requiring the manufacturer to produce data showing that the ultrasound device effectively differentiates between a cancerous and benign lesion. Without data clearly demonstrating the effectiveness of ultrasound for this use, many women could have cancerous lumps misdiagnosed as benign, and thus forgo early lifesaving treatment.

Limiting Consideration of Certain Effectiveness Data. For the more complicated devices that actually would remain subject to FDA review under H.R. 3201, the bill includes the same effectiveness determination limitation as the drug bill. The concerns expressed regarding the drug bill's limitations on evaluating comparative efficacy and uses not included in the labeling apply equally to devices. In addition, Section 8 of H.R. 3201 prohibits FDA from evaluating clinical outcomes for devices, unless the device is labeled as having a therapeutic effect. It appears that the Agency would be prohibited from looking at whether devices really help patients -- for example, whether patients with artificial hearts did well or died prematurely -- unless the outcome is part of an explicit labeling

claim. This emasculates the present system that requires certain devices be shown to clinically perform as intended and produce useful outcomes for patients and ultimately will impair clinical decision-making by health care providers.

Manufacturing Changes. As with drugs, FDA's responsibility for safe products does not end when a device is approved by FDA. Manufacturing changes can greatly impact the safety of medical devices. Section 9 would permit manufacturers to make significant manufacturing changes to devices subject to the 510(k) provisions without first coming to FDA. Section 11 of the device bill would eliminate the need for PMA supplements for changes that "do not actually affect device safety or effectiveness." In effect, this relieves manufacturers from seeking FDA approval for certain changes in manufacturing processes, sites of manufacture, sterilization procedures, etc. The risk is that a manufacturer will determine that a change does not affect safety or effectiveness, when in fact, it does.

Decreased Ability to Monitor Marketed Devices. The Safe Medical Devices Act of 1990 added a number of provisions to the FDC Act designed to enable FDA to monitor devices after they were sold. Specifically, it added a requirement for device tracking to enable FDA or the manufacturer to quickly and efficiently alert patients if a device subsequently proves faulty and presents serious health risks. It also added a post marketing

surveillance provision to supplement the approval process because Congress felt that premarket approval could not detect all possible problems that might occur after a device is put into general use. Finally, it added a requirement for user reporting because there were device injuries occurring in hospitals that were never reported to FDA. H.R. 3201, however, eliminates user reporting and significantly curtails FDA's ability to monitor marketed devices under the other two provisions.

For example, section 14 severely restricts FDA's ability to require device tracking. Specifically it changes the criteria for a tracking requirement, and it eliminates FDA's discretion to apply the provision to "any other device." FDA used this "discretionary" authority to require tracking of implantable infusion pumps, silicone breast implants, and other silicone related devices. The legislation will eliminate our ability to track devices the failure of which could have significant public health implications.

Section 15 limits the type of device that can be the subject of postmarket surveillance. The most problematic aspect of this provision is that it only permits FDA to require postmarket surveillance for devices "first introduced or delivered into interstate commerce after January 1, 1991." This would preclude FDA from requiring postmarketing surveillance of devices such as the Shiley heart valves, Landmark catheters, and foam-coated

breast implants -- all products shown to subject their users to health risks.

4. H.R. 3200 -- Foods and Animal Drugs

Delaney Clauses. For more than 35 years, consumers have known that manufacturers are not permitted to add to food for human consumption or food and color additives that have been shown to induce cancer. Manufacturers have had the burden of proving that additives or animal drugs used in livestock are safe. The Delaney clauses were premised on a simple public-health principle: Because the public is exposed to many sources of cancer risk (many unavoidable and involuntary), this risk should not be increased by intentionally adding carcinogens to food.

H.R. 3200 would change the long-standing safety standard to which food and color additives that have been held for almost 40 years. H.R. 3200's safety standard of negligible, de minimis, or insignificant risk would result in the intentional addition to the diets of American consumers carcinogenic food and color additives that heretofore have not been permitted. Furthermore, this change, whatever negative public health impact it might have on its own, must be considered in the context of another significant safety-related change proposed in H.R. 3200. Under the bill, when a food or color additive is reviewed by a third party, the burden of proof shifts from the manufacturer, in whom

the responsibility for safety demonstration has resided since 1958, to the FDA. In such circumstances, to prevent the marketing of a carcinogen intentionally added to food, the Agency would be required to show that the additive causes a significant cancer risk or that there otherwise is a reasonable probability that the additive is unsafe. It is clear that these provisions ask the American public to take on additional risk from foods without any concomitant benefit.

Although FDA is willing to consider changes to the Delaney clause, our overall focus must remain on assuring that the public is adequately protected. As you know, the Administration has recommended, and I have supported, legislation that would remove pesticide residues from consideration under the Delaney clause. That change was recommended only because it was coupled with other changes to the overall regulatory scheme for pesticides, including the creation of a higher, risk-only, health-based standard for residues along with provisions that would assure a more careful consideration of the effects of pesticide residues on infants and children. In proposing to eliminate the Delaney clause, H.R. 3200 not only fails to provide these extra measures of safety and public assurance, but, as noted, actually weakens the safety standard for food and color additives and makes it more difficult for FDA to deny approval to an additive that, according to the Agency's assessment, has not been shown to be safe. Thus, under the bill, the protection afforded to consumers

from unsafe additives falls short of that proposed by the Administration for pesticide residues and that provided by current law.

Preemption. H.R. 3200 prohibits states from establishing requirements (including prohibitions) for a food, drug, or cosmetic that relate to FDA's adulteration, misbranding, or new drug authority if it is not identical to a requirement authorized or required by the FDC Act. It also prohibits states from imposing any notification requirement for a food, drug, or cosmetic that provides for disclosure of the constituents, source, or method of production or processing such product or for a warning concerning the safety of the product or any component or package thereof unless such requirement is identical to a requirement prescribed under the FDC Act.

The effect of this sweeping preemption provision is to take away states' authority to impose requirements to ensure the safety of the food, drug, and cosmetic supply. It basically would place this responsibility totally in the hands of the federal government. Thus, if the state of California wanted to require the maker of Rio hair dye, which caused users' hair to fall out, to warn consumers, or the state of Texas wanted to require a warning on ephedra, they could not unless the Federal government had identical warning requirements. Moreover, at the same time this legislation is transferring all responsibility to FDA, it is

weakening FDA's ability to fulfill that responsibility. For example, together the Delaney clause provision and the third party review provision undermine FDA's efforts to ensure the safety of the American food supply. This provision also could have the effect of preempting state personal injury lawsuits involving foods, drugs, and cosmetics. (Compare Medtronic, Inc. v. Lohr v. Medtronic, Inc., 56 F.3d 1335 (11th Cir. 1995), cert. granted, 64 U.S.L.W. 3497, 3500 (U.S. January 19, 1996) (Nos. 95-754, 95-886) and cases cited therein.)

Finally, a problem with the preemption provision, in the food area in particular, is that there are certain areas (such as grocery stores and restaurants) that, partially due to FDA resource constraints, have traditionally been regulated by states and localities. State and local regulations are critical to protecting the public health. Frequent inspections by state and local authorities ensure that restaurant and nursing home kitchens are sanitary and that food is handled safely. The states are responsible for ensuring that the fast food hamburgers we so often enjoy have been cooked at the appropriate temperature. Yet, under H.R. 3200, they may no longer have that authority. Because of the prohibition in the bill, some areas that significantly impact the public health could be virtually unregulated.

Increased Risks From Minor Animal Species Receiving Ineffective Drugs. This legislation would adversely affect the public health, not only because of the bills' impact on the regulation of drugs, devices, and foods, but also because of H.R. 3200's impact on animal drugs. For example, H.R. 3200 would eliminate the requirement to show effectiveness of animal drugs intended for uses in minor species or for minor uses. Elimination of a requirement to show effectiveness takes us back to before 1962. There is no point to having drugs that cannot be shown to be effective. Moreover, the availability of ineffective animal drugs has implications for both animal and human health. The use of ineffective animal drugs in minor species or for minor uses can lead to the unnecessary suffering and death of animals and an increase in the potential for the transmission of diseases from animals to humans. It may also increase the potential for development of bacterial resistance to antibiotics.

Combination Animal Drugs. H.R. 3200 also changes the standards for approving combination animal drugs. It would permit a sponsor to market a combination animal drug containing two or more drugs that are targeted to the same indication without having to show that each drug provides some additional benefit. Moreover, it would not require the sponsor of a combination animal drug to establish the safety of the combination to the animal targeted to receive the combination.

Prior to enactment of the current animal drug laws, manufacturers marketed drugs that contained significant amounts of multiple powerful antibiotics to treat infections in milk cows without showing that each antibiotic added to the effectiveness of the drug. The marketing of similar products today, as the bill would permit, increases the risk of antibiotic resistance, which could result in less effective human antibiotics, and could lure farmers into paying for drugs that are unnecessary and dangerous.

Dangerous Animal Drug Residues. One final provision that would affect the public health by eliminating certain animal drug protections is in the drug and device bills. Both add a new section 909 to the FDC Act that prohibits FDA from limiting or interfering with a health care practitioner's authority to prescribe or administer legally marketed drugs or devices. This provision appears to interfere with FDA's current authority to restrict a veterinarian's use of certain animal drugs in food producing animals on the grounds that such use could adulterate the food supply.

For example, chloramphenicol is an antibiotic currently approved for use in non-food producing animals to treat respiratory and urinary tract infections. It has not been approved for use in food producing animals because it is associated with severe side effects (e.g., aplastic anemia and death). Under new section 909, however, a veterinarian could prescribe chloramphenicol in

food producing animals. Persons who consume the meat from those animals would be exposed to the chloramphenicol and its adverse side effects.

C. ALL THREE BILLS WOULD UNDERCUT CURRENT EFFICACY STANDARDS AND INCREASE THE POSSIBILITY OF INEFFECTIVE AND UNSAFE PRODUCTS REACHING THE MARKET

The privatization provisions that appear in all three bills would lower the approval standards for products subject to third party review. A number of additional provisions in the bills lower the efficacy standards for products regardless of whether they are subject to third party review.

Common Medical Practice. Section 5 of the drug bill would permit the approval of a new use of a previously approved drug on the basis of a demonstration that the new use is common among clinicians experienced in the field and represents reasonable clinical practice based upon reliable clinical experience and confirmatory information. Basically, the bill assumes that if many doctors prescribe a drug for a particular unapproved use, then that unapproved use must work.

A drug may come into widespread use for a condition because common experience suggests that the drug seems to work. Unfortunately, experience shows that testing in clinical trials

often demonstrates that the drug is not effective and in fact, may be harmful. Medical history is replete with examples of products and procedures that were based on medical anecdote, not evidence, and were thought for years by most clinicians to be effective, but later turned out to be useless and sometimes dangerous. It may be hard to believe, but clinical experience often provides the wrong answer.

For example, in the late 1980's, physicians began to prescribe the drugs encainide and flecainide, for heart attack victims who were experiencing ventricular premature complexes (VPCs), a type of asymptomatic or minimally symptomatic abnormal rhythm of the heart. This off-label use for these drugs, which were approved for other types of abnormal heart rhythms, was intended to prevent the increased mortality of heart attack victims. The use became so widespread that the National Institutes of Health decided to study it. At the time, everyone was so sure that the drugs worked for the new use that it was thought to be unethical to conduct a controlled clinical trial because that would mean that certain patients would not receive encainide or flecainide. To nearly everyone's surprise, that study demonstrated not only that the drugs were ineffective in reducing the risk of death, but also that the drugs were actually harmful in the patients for whom they were being prescribed off-label. This bill would permit unproven uses such as this to get onto the drug label.

This legislation would move us away from the accepted scientific standard of evidence and back towards evidence based solely on anecdotal experience. Anecdotal reports and poorly controlled observations have proven not to suffice because they can be wrong. We know this because, in 1962, Congress told us to take a hard look at the drugs that entered the market prior to the addition of the efficacy standard to figure out which ones actually worked and which ones did not work, but were still being prescribed by doctors. With the assistance of the National Academy of Sciences, FDA looked at the objective scientific information available on 3,443 drugs. The result of this review found that only one-third of the drugs really worked. The other two-thirds either were not effective, despite the beliefs of physicians, or could not be shown to be effective.

H.R. 3199 would perpetuate the kind of inappropriate and unproven medical practices that existed prior to 1962. It also could have the unintended consequences of creating a disincentive for companies to collect the scientific data necessary to demonstrate whether a product is effective for a particular use.

We must ask ourselves, is it a good idea to go back to the pre-1962 era and permit drugs to be labeled for uses if some doctors think they work for those uses, or are we better off with the current system where there are incentives to do the studies to find out scientifically whether the drugs work for new uses? FDA

is on the side of getting the scientific information. The public has a right to drugs that actually work as intended.

Approval of Drugs for Serious and Life Threatening Diseases. Section 5 of the drug bill also provides that an application for a new drug for a serious or life-threatening condition shall be considered to have substantial evidence if it could fairly and responsibly be concluded by experts that there is a reasonable likelihood that the drug will be effective in a significant number of patients and that the risk from the drug is no greater than the risk from the condition.

This provision undermines the efficacy standard and shifts the risk analysis away from risk/benefit. FDA strongly supports getting drugs for serious and life threatening diseases to patients as quickly as possible. The Agency has developed a process to accelerate approval of drugs for serious and life-threatening diseases, by approving such drugs for marketing before the data from traditional clinical trials are complete if the drug shows an effect on a "surrogate marker." Thus far, this has been proving to be a successful process. FDA does not and cannot, however, support a provision that would allow approval of a new product that has not been adequately tested.

Product Approval Standards. All three bills contain provisions that explicitly lower the efficacy standard. Section 5 of the

drug bill provides that "one or more" clinical investigations may be needed to show effectiveness. The Agency's current presumption is that, for pharmaceuticals, ordinarily, replicated evidence is expected, but FDA, in particular circumstances (i.e., where a single study offers internal evidence of consistency of the product's effectiveness), may rely on a single adequate and well-controlled trial. The provision, on its face, does not appear to change that presumption. However, we understand that its purpose is to create a presumption that one adequate and well controlled trial will be sufficient for purposes of approving a new drug.

The Agency strongly opposes a change that would eliminate the replication requirement for drug approval. It is a basic tenet of science that data can be considered reliable only if, when an experiment is run for the second time, it produces the same findings and observations that it produced the first time. The American public deserves to receive drugs that have been tested according to well accepted scientific principles.

Section 8 of the device bill changes the current effectiveness standard to include a maximum of one clinical investigation and establishes that no clinical investigation will be required unless the Secretary first consults with a classification panel. Because devices, unlike drugs, have the mechanism of action designed into them, the need for demonstrated replication has not

been a part of the way we have reviewed clinical data on devices over the last 20 years. Nevertheless, in those cases where the devices mechanism of action is poorly understood, replication of clinical data is correspondingly important.

Finally, section 201(a) of the animal drug bill redefines the "substantial evidence" criteria that currently must be met to establish efficacy. The provision changes the substantial evidence requirement from adequate and well-controlled studies to scientifically sound studies. The requirement that the studies fairly and reasonably show effectiveness has been changed to a requirement of a reasonable assurance of efficacy. The provision also eliminates the requirement for field investigations unless FDA justifies in writing the need for such investigations to show the effectiveness of animal drugs. This lower standard for effectiveness for new animal drugs is not acceptable.

Off Label Use. The drug and device bills make it legal for a sponsor to disseminate medical texts, journal articles, and government information, and to make presentations at medical and scientific meetings and have displays at trade shows about off-label uses.

These provisions assume that the various activities it permits are not promotion and do not encourage off-label uses or uses of investigational products. Their effect, however, is to make it

possible for sponsors to promote off-label uses and investigational products.

FDA knows that there are important off-label uses of approved products. In this context, it is important that physicians have access to accurate information about drugs and devices. But we also know that allowing the promotion of these kinds of uses by companies with a financial interest in the products' use can have very serious public health consequences.

The fundamental problem with permitting the promotion of off-label uses is that not all off-label uses help patients; some do not work and some are harmful. The only way to know which ones are safe and effective is to collect and analyze the data supporting a finding of safety and efficacy. Permitting the promotion of off-label uses based on studies reported in journal articles or other texts or unpublished materials, which clearly are an inadequate basis for approval, would undermine the efficacy standard.

One of the most serious consequences of allowing companies to promote off-label uses is that companies would have no incentive to conduct or fund the necessary scientific research and to present data to FDA to verify the safety and efficacy of those off-label uses. In fact, because the Agency might determine that the new use is not supported by the evidence, there would be an

incentive to avoid FDA review. For devices, the incentive problem is exacerbated because the investigational device provisions (Section 4) would permit more widespread use of investigational products, which the sponsors can now promote and for which they can be compensated.

If off-label uses could be promoted, manufacturers would have an incentive to do the minimal number of studies necessary to obtain approval for the first, narrowest/easiest indication and then heavily promote the product for other broader -- and possibly more speculative -- uses. For example, interferon-alpha 2b was approved for use in hairy cell leukemia, of which there are approximately 300-400 cases per year. It subsequently was approved to treat chronic hepatitis B and C, of which there are tens of thousands of cases per year. If the manufacturer of interferon alpha 2b could have promoted the product for chronic hepatitis B and C -- the much broader use -- based on preliminary data, we might never have learned whether interferon alpha 2b actually works to treat hepatitis B and C.

Because the incentive to conduct research on uses of drugs and devices will decrease, the end result will be that the dissemination of off-label information will actually reduce the amount of good scientific information that health care providers receive about drugs and devices.

Widespread promotion of unapproved uses also raises significant safety concerns. Even under current law, which prohibits the promotion of off-label uses, we know of a number of instances where physicians have used drugs for off-label uses that have resulted in disastrous consequences. The off-label use of encainide and flecainide, discussed earlier, was supported by published peer-reviewed journal articles. If the unapproved uses had been heavily promoted by drug companies, it is estimated that thousands more unnecessary deaths would have occurred.

The current law governing promotion requires balance. Changing the law to allow the distribution of journal articles and other similar materials that promote off-label uses will allow drug sales representatives to provide materials that describe favorable study results of their product for a particular use, without providing copies of materials that demonstrate the other view. What makes this situation even more troubling is that when FDA has evidence that a particular use is unsafe or ineffective, federal confidentiality laws frequently inhibit our ability to disseminate that information. Thus, there are off-label uses about which positive studies appear in the literature and negative data are contained in our files. Depending on its source, FDA may be unable to use the negative information to ensure that the medical community and the public have all of the available facts on which to base treatment decisions. At the very least, it is irresponsible to open up promotion of off label

uses without giving the Agency explicit authority to rebut that promotion.

FDA recognizes that there are important off-label uses. We believe, however, that the best way to address concerns that information about those uses is not reaching medical practitioners is to get those uses for which the drug actually works in the labeling. As you know, a subsequent indication for a new drugs is added via a supplemental new drug application, which often needs to present only efficacy information to support that new use.

FDA has been developing ideas for encouraging and expediting efficacy supplements for unapproved uses. These include: taking steps to help expedite the review of efficacy supplements; clearly explaining what data is needed for efficacy supplements for new indications; and seeking out the most appropriate off-label uses and getting them onto the label.

D. H.R. 3200 ROLLS BACK THE PROGRESS MADE BY THE NUTRITION LABELING AND EDUCATION ACT OF 1990

In 1990, Congress passed the Nutrition Labeling and Education Act (NLEA). The driving force behind the NLEA was the desire to end consumer deception and to help consumers in choosing a healthful diet. Among other things, the NLEA sought to ensure that claims

about the nutrient content of foods (e.g.,"high in vitamin C") would make sense to consumers and that consumers would receive accurate information about the health benefits of foods. The NLEA accomplished these goals by defining nutrient content claims and by requiring that FDA review proposed diet/disease claims to ensure that there is an adequate scientific basis for the claim. H.R. 3200 not only significantly rolls back the progress that NLEA made on both of these fronts, it also undermines our ability to provide information to consumers by limiting the type of information we can require on the food label. For example, section 104 limits our ability to require disclosure of a method of production or an ingredient.

Synonyms. The NLEA sought to make sense out of the panoply of nutrient content claims on food labels, by standardizing the terms that could be used. Only those descriptors defined by FDA (through notice and comment rulemaking) (e.g., "low", "good source of" or "high") could be used. H.R. 3200 amends that provision to permit synonyms of those defined terms, provided only that they are not false or misleading.

The bill allows food manufacturers to determine appropriate synonyms. There is no standard for companies to meet before using a new descriptor and the burden would be on the Agency to prove that a term is not a synonym for a defined term or that the term is false or misleading. This provision could result in a

large increase of nutrient content descriptors. The uniformity and clarity that the NLEA created would be lost. The resulting plethora of uncontrolled terms would confuse consumers by diminishing the educational value of the defined terms. For example, is "lots of fiber" a synonym for "excellent source of fiber" or "good source of fiber"? The use of such vague terms would permit marketers to expand the market by blurring the distinctions between the nutritive value of different products.

FDA's current regulations permit a company to petition for the use of synonyms. In addition, FDA recently proposed to amend its nutrient content claim regulations to permit manufacturers to use synonyms of defined nutrient descriptors as long as such synonyms are not false and misleading and the synonym is "anchored" to the defined term -- i.e., the defined term appears prominently on the label. The Agency's proposal properly balances the concern of unbridled uses of synonyms that can lead to consumer confusion with industry's need for greater flexibility to market the healthful aspects of their products.

Health Claims. H.R. 3200 would allow any materials prepared or distributed by any federal health agency or by the National Academy of Sciences to serve as the basis for a health claim -- i.e., to fulfill the significant scientific agreement requirement.

The provision is vague and overly broad. The bill would appear to allow ANY information prepared for whatever reason (i.e., not specifically for the purpose of evaluating a diet/disease claim relationship) to form the basis of a health claim. For example, materials relating to a particular diet/disease relationship prepared and distributed as background for a hearing by the NAS or a briefing by NCI could be used as the basis for a health claim. Moreover, information contained in pamphlets written by a private organization and distributed by a Federal health agency or the NAS could form the basis for a health claim under this provision. Information could be taken out of context. Finally, there appears to be no remedy for FDA if it disagrees with a claim evaluation made by another agency. FDA would be unable to require a private or public debate about the meaning of the data or information that is relied upon to make the diet/disease claim.

This provision fundamentally alters the criteria for health claims that were so carefully worked out in the Nutrition Labeling and Education Act of 1990. Under the bill, there would be no single body to make decisions on health claims. Because there may be inconsistent decisions by different organizations using different standards, we would see the type of consumer confusion and misinformation that was rampant before passage of the NLEA. Even worse, we may see cases where claims that come from information prepared or distributed by a federal health

agency or the NAS are just wrong. For example, although reports and recommendations of certain federal health agencies and the National Academy of Sciences indicated that beta-carotene prevents lung cancer, subsequent studies found not only that beta-carotene was not effective in reducing the risk of cancer, but that for some persons (e.g., smokers) it actually increased their risk of cancer and death.

E. THE REFORM BILLS WOULD INCREASE BUREAUCRATIC REQUIREMENTS WITHOUT PROVIDING ADDITIONAL RESOURCES

All three bills impose significant, new administrative burdens. For example, they require the Agency to hold numerous meetings throughout the review process and to provide detailed written responses to sponsors on virtually any issue that may arise throughout the review process. They also require the Agency to establish a dispute resolution process, which duplicates existing mechanisms, and they subject virtually any FDA decision about drugs to judicial review (thus, threatening to paralyze the Agency with useless litigation).

The excessive burden imposed by the bills is perhaps best illustrated by a provision in the device bill. Section 11 first creates thirteen new deadlines, many of which are unreasonably short. And then, having created these deadlines, which we probably cannot meet, it requires a report be submitted to the

Commissioner and the Secretary every time a deadline (including one of the eight interim deadlines) in the bill is missed. The Commissioner then has 10 days to provide an explanation to the applicant of the reasons for failure to meet the deadline. The Secretary must submit an annual report to Congress that summarizes each of these missed deadlines. This provision takes deadlines and reporting to the extreme.

CONCLUSION

Mr. Chairman, I have spent the past five and a half years pushing very hard to get safe and effective products to patients as quickly as possible. We have a strong foundation on which to build: the Prescription Drug User Fee Program, the efforts that have been made under the Administration's reinventing government initiative, and our successes in expediting development and approval of drugs for life-threatening illnesses.

The problem we see with the three bills now being considered is that too often they try to solve yesterday's problems with untested solutions. Our concern is that these measures, if enacted into law, would not only do little to actually help FDA get products to patients faster they would undermine our ability to protect American citizen's from unsafe and ineffective products.

Be assured, that the FDA and the Administration will continue to push for change, but the right kind of change. We look forward to continuing to explore new ideas on how to best assess new product effectiveness, how to get products labeled to reflect the best data on their use, how to facilitate clinical development and how to get the Agency's independent review of new products done expeditiously so that important scientific advances move to the bedside more quickly.

Thank you.

THE FOOD AND DRUG ADMINISTRATION'S REINVENTING GOVERNMENT INITIATIVES

The Food and Drug Administration (FDA) is committed to making government work better by reducing unnecessary regulatory burdens while maintaining the critical public health protections that the American people expect and deserve. The agency has been reviewing its regulatory processes to determine which requirements could be reduced or eliminated without lowering health and safety standards. Over the past year, FDA has worked with the Vice President's National Performance Review as well as other agencies to develop four reports that detail many initiatives that will result in less burden on industry and FDA and will ultimately speed up product approvals and increase access to new products.

DRUG AND MEDICAL DEVICE REPORT

The first report, Reinventing Drug and Medical Device Regulations, was released in April 1995. During the development of these initiatives, the agency followed four principles: expedite review without sacrificing the health and safety of the public; use performance standards whenever possible; eliminate unnecessary requirements that may have once been appropriate but are now outdated; and utilize automated technology as a tool to streamline management and an aid to industry. The reforms in the drug and device report are estimated to save the drug and device industries $500 million per year in unnecessary regulatory costs. These reforms will also let FDA better target its resources toward expedited market access of safe and effective new products. The reforms detailed in this report are the following:

- **MANUFACTURING CHANGES**--Allowing manufacturers of drugs and biologics to change the way they manufacture an approved drug without FDA pre-approval if the risk is negligible.

IMPACT: Industry can modernize facilities and processes more easily; FDA can shift resources to more critical review needs.

- **BIOLOGICS PILOT FACILITIES**--Clarifying that manufacturers of biological drugs may get licenses for pilot facilities instead of building full-scale manufacturing plants.

IMPACT: Manufacturers have lower start-up costs and can more quickly begin production of new biological products.

- **BIOLOGICS LABELING REQUIREMENTS**--Permitting greater flexibility in how distributors' names appear on biological product containers, package labels, and labeling.

IMPACT: Companies, in particular small, start-up biotechnology firms, may more readily enter into manufacturing, packaging, and distribution arrangements and thereby bring products to market more quickly.

- **ANTIBIOTICS/INSULIN**--Supporting repeal of special statutory requirements for manufacturing insulin and antibiotic drugs.

IMPACT: Industry would no longer be burdened with outdated requirements and FDA could regulate these products the same way it does other drugs. Elimination of these requirements remove nearly 700 pages from the CFR.

- **ENVIRONMENTAL ASSESSMENTS**--Excluding drug and biologics manufacturers from the requirements to prepare environmental assessments (EAs) for most products.

IMPACT: Industry will be spared the expense of preparing assessments that FDA has found unnecessary--estimated at between $40,000 and $150,000 per EA. FDA will not have to spend resources reviewing EAs for products that will not have a significant effect on the environment.

- **MEDICAL DEVICE EXEMPTIONS**--Exempting up to 122 categories of low-risk medical devices from premarket review, adding to the 450 categories already exempted from review.

IMPACT: Industry no longer has to wait for premarket review for these devices, meaning that they can reach patients sooner. FDA can shift resources to more critical review needs.

- **MEDICAL DEVICE "REFERENCE LIST"**--Eliminating the "reference list" (an FDA tracking system for device manufacturers who have had serious manufacturing violations) and clarifying that premarket review of medical devices can be affected only if good manufacturing practice violations are related to a specific device.

IMPACT: Industry concerns that good manufacturing practice violations for one

product can slow down approval for other devices unrelated to those problems is alleviated, and there is more certainty about when products can be marketed.

- **MEDICAL DEVICE PILOT PROGRAM**--Developing a pilot program for the review of low-to-moderate risk medical devices by outside organizations.

IMPACT: This program will help determine if such a system can speed the review of these devices while maintaining public health protection, whether the independence of the review process can be maintained, and if such a system will be less costly.

- **MEDICAL DEVICE USER FEES**--Speeding the marketing of medical devices by requesting a change in legislation to authorize charging industry user fees to give FDA more resources for product reviews and committing FDA to strict performance goals.

IMPACT: This program would address complaints about review times for medical devices. A similar program for prescription drugs, the Prescription Drug User Fee Act (PDUFA), has substantially reduced review times and FDA has met all performance goals to date.

- **DRUG AND DEVICE EXPORTS**--Expanding the opportunities for the export of unapproved drugs and medical devices to industrialized countries while leaving intact existing protections for countries that are not industrialized.

IMPACT: Industry will have wider markets for its products and will be encouraged to maintain operations in this country. FDA can redirect resources used for the current export approval program to more pressing health matters.

- **EFFECTIVENESS OF DRUGS AND DEVICES**--Clarifying the effectiveness standard for new drugs and devices.

IMPACT: Industry will have a better understanding of how to develop new products, reducing the time it takes to bring a drug or device to FDA for review.

- **INTERNATIONAL HARMONIZATION**--Working with the EU, Japan, and NAFTA partners to harmonize product testing and development standards for drugs and medical devices.

IMPACT: The worldwide marketing of new products will be expedited if there is

less need for duplicative testing to meet the standards of different countries.

- **SMART TRACKING SYSTEM**--Facilitating the development of information systems to support review processes.

IMPACT: As electronic document management and automated review tools are developed and implemented, regulated industry will achieve greater internal efficiencies in its development and formatting of submissions. Both industry and the FDA will have reductions in the costs of information handling, storage, and retrieval.

- **OASIS SYSTEM**--Developing an information systems initiative, Operational and Administrative System for Import Support (OASIS), to support automation of the import clearance process.

IMPACT: FDA resources that were once used to handle and review paperwork regarding shipments can now be focused on the shipments that fail to meet FDA standards, thus benefiting the American consumer.

DRUGS MADE FROM BIOTECHNOLOGY REPORT

In November 1995, FDA released a second report entitled, "Reinventing the Regulation of Drugs Made from Biotechnology." The changes in the report represent the most significant overhaul of the regulation of biotech drugs FDA has ever attempted. In these reforms, FDA in essence harmonizes its regulation of biotech drugs that qualify as "well-characterized," making uniform the requirements of its two product centers responsible for helping to ensure the safety and effectiveness of biologic drugs: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). According to the biotechnology industry, these changes will save their companies millions of dollars, reduce the required paperwork by thousands of pages, and cut drug development time by months. At the same time, the agency believes that these modifications will not diminish the safety and effectiveness of biotech drugs. The changes detailed in the report are the following:

- **ESTABLISHMENT LICENSE APPLICATION**--Eliminating the requirement for submission and approval of establishment license applications for biotech drugs that are "well-characterized." The amount of information that companies will need to provide in the product license application will also be reduced.

IMPACT: Biotech drugs will get to market faster and companies will be able to devote more resources to developing drugs and ensuring that they are manufactured appropriately--this will especially benefit small biotech companies that lack experience in filing applications.

- **LOT RELEASE**--Once a well-characterized therapeutic biotech drug has been licensed for marketing and its manufacturing process has been validated, it will not be subject to lot-by-lot release by the FDA.

IMPACT: The elimination of lot release will result in a significant savings of time and resources for both the industry and the agency.

- **HARMONIZED APPLICATION FORMAT**--Consolidating the current 21 application forms for establishment license, product license, and new drugs into one standardized form.

IMPACT: Companies will be able to provide higher quality submissions and industry time to prepare applications will be reduced.

- **PROMOTIONAL LABELING**--Revising policy so that biotech companies will no longer have to submit their promotional labeling to FDA prior to the launch of a new biologic.

IMPACT: Industry will no longer have to await approval of promotional labeling prior to disseminating it; agency resources will be freed up to accomplish other review activities.

- **CLINICAL HOLDS**--Committing to review and respond to data submitted in response to a clinical hold (a directive issued by FDA that prevents the clinical study from proceeding) within 30 days of receiving the submission.

IMPACT: This initiative will prevent delays in agency review of data, thus preventing unnecessary delays in the start or continuation of clinical studies.

- **RESPONSIBLE HEAD REQUIREMENT**--Changing policy so that biotech companies will no longer have to designate one person as a "Responsible Head" who deals with the FDA in all matters relating to compliance with the regulations and who represents the manufacturer in all dealings with the FDA.

IMPACT: This will allow industry more flexibility to assign control and oversight responsibility within a company. The appropriate individuals can communicate directly with the agency on official matters regarding the products that they manufacture.

FOOD REGULATIONS REPORT

In January 1996, the Food and Drug Administration released another report, "Reinventing Food Regulations," which was done in conjunction with the Department of Agriculture and the Department of Commerce. FDA oversees a vast food industry that includes about 46,000 U.S. food processors and warehouses, and comprises a significant segment of the nation's economy. FDA-regulated products account for about two-thirds of consumer spending on food, with an annual retail value of $430 billion. Every year, food processors spend $1.4 billion on research and development and introduce 15,000 new products. FDA's food-related regulations address many public concerns, including: pathogens; chemical contaminants; wholesomeness; misbranding; economic deception; and safety of food and color additives. In addition, FDA is responsible for setting standards for safe and sanitary production of food, resolving issues involving imported foods, and advising state and local governments on safety and sanitation standards for supermarkets, restaurants, and other retail food establishments. FDA also regulates animal drugs, medicated feeds, and animal feed additives, all of which may affect the human food supply. The reforms detailed in the Foods report are listed below.

- **SEAFOOD HACCP**--Adopting a preventative system of quality control known as HACCP (Hazard Analysis and Critical Control Points) which relies more on seafood companies to devise and implement performance standards and food safety plans uniquely suited to their needs. This system replaces the old system of detecting and correcting problems after they occur, with a system of preventing them in the first place.

IMPACT: The program will improve the safety of seafood by building the principle of prevention into food production operations and stimulating improvement in safety practices by setting reasonable performance standards.

- **FOOD ADDITIVE PETITIONS**--Reforming four elements of the food additive petition process: (1) establishing and meeting deadlines for action on petition reviews; (2) reducing pending-petition inventory; (3) testing and instituting new approaches to review; and (4) implementing management reforms within the food additive review program.

IMPACT: The proposed solutions will address major complaints about food additive review procedures and response times. The food ingredient industry will benefit from shorter review times, will be able to market more new and innovative products faster, and will become more competitive in foreign markets.

- **GRAS SUBSTANCES**--Establishing a notification procedure that gives companies a greatly simplified process by which to notify FDA of their independent GRAS (Generally Recognized As Safe) determinations for products.

IMPACT: Industry would realize significant savings through elimination of the time and expense associated with assembling large and complex GRAS-petition packages. Savings to industry could range from thousands to hundreds of thousands of dollars, depending on the food ingredient involved.

- **MEAT AND POULTRY ADDITIVES**--Changing policy to eliminate duplicative review of food and color additives in meat and poultry. FDA and FSIS (Food Safety and Inspection Service at the Department of Agriculture) will enter into a memorandum of understanding under which the two agencies will work together so that use of food and color additives in meat and poultry will require only FDA approval.

IMPACT: This will provide for a simpler, quicker, and more coherent approval process for food and color additives in meat and poultry. This initiative will also eliminate some unnecessary and burdensome restrictions on industry.

- **FOOD STANDARDS OF IDENTITY**--Eliminating or simplifying many of the detailed requirements of food standard regulations.

IMPACT: FDA is seeking to increase the flexibility of food standards to provide, for example, for the use of ingredients to meet consumers' dietary preferences without undercutting the assurance of a high quality food supply that is provided by food standards.

- **HARMONIZATION OF STANDARDS**--Working with other countries including Canada, Mexico, and the European Union to harmonize food and animal drug safety standards.

IMPACT: This initiative increases the safety and quality of food imported into the U.S. and can improve the safety and quality of foods produced and sold in foreign

countries.

- **PRIVATE LABS**--Working to develop pilot programs that make better use of private and state or local laboratories for analyzing food imports.

IMPACT: The development of pilot programs will enable the agency to learn how best to make further use of non-FDA labs for monitoring and analyzing imported foods.

- **ANIMAL DRUG EXPORTS**--Allowing the export of animal drugs, whether or not they have been approved in the U.S., to any country so long as the exported product has been approved for marketing in the receiving country.

IMPACT: U.S. manufacturers of animal drugs will be able to expand their markets and, consequently, may be more likely to locate animal drug manufacturing facilities in the United States.

- **APPLICATION FOR ANIMAL DRUG RESIDUES IN IMPORTED FOOD**--Changing the way that the agency reviews animal drug applications for use abroad so that the agency will focus its reviews on the safety of drug residues in imported food products.

IMPACT: Under this initiative FDA would use administrative processes or seek legislative authority to eliminate, or make less burdensome, an unnecessary approval requirement and would advance in the direction of international harmonization of regulatory requirements.

- **ENVIRONMENTAL ASSESSMENTS**--Reducing the number of environmental assessments required to be submitted by industry for animal drugs, animal feed additives, food additives, and color additives.

IMPACT: This change will benefit industry and will improve regulatory efficiency without having any adverse impact on public health or the environment.

- **MEDICATED FEED APPLICATIONS**--Eliminating medicated feed applications and allowing any medicated feed containing an approved new animal drug to be manufactured at a licensed facility.

IMPACT: Elimination of medicated feed applications (MFAs) would result in an estimated savings to industry in excess of $1 million per year, and a savings to FDA of $200,000 yearly that is currently allocated for the processing of MFAs by a contractor.

CANCER DRUGS REPORT

In March 1996, the FDA released a fourth reinventing government report, "Reinventing the Regulation of Cancer Drugs: Accelerating Approval and Expanding Access." The Food and Drug Administration has demonstrated a longstanding commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. The initiatives detailed in the report are below:

- **ACCELERATED APPROVAL FOR CANCER DRUGS**--Expanding the use of the accelerated approval process for cancer treatments, based upon verified tumor shrinkage, as opposed to other criteria such as survival, improved quality of life, and relief of symptoms.

IMPACT: This policy makes it easier to study cancer therapies and shorten the total time for first and subsequent marketing approvals for a wide range of cancer therapeutics. Patients will have access to promising cancer therapies at an earlier time than was previously possible.

- **EXPANDED ACCESS**--Encouraging sponsors of experimental drugs that have been approved in certain other countries to apply for permission to distribute the drug to eligible cancer patients before final drug approval has been granted. For patients with serious and life-threatening illnesses such as cancer, FDA has devised several programs that provide access to promising but unapproved therapies even as they are being studied.

IMPACT: This policy helps to make experimental cancer therapies available to patients shortly after they are approved in other countries even if they are in the early stages of their U.S. development.

- **INCREASED CANCER PATIENT REPRESENTATION**--Including one person who has experienced the specific cancer being discussed on each cancer-therapy advisory committee. FDA relies on advisory committees to provide outside expertise on agency policy and product decisions. Because cancer is not just one disease but many, more representation will be given to cancer patients.

IMPACT: This initiative improves FDA's policy of including patient perspectives on

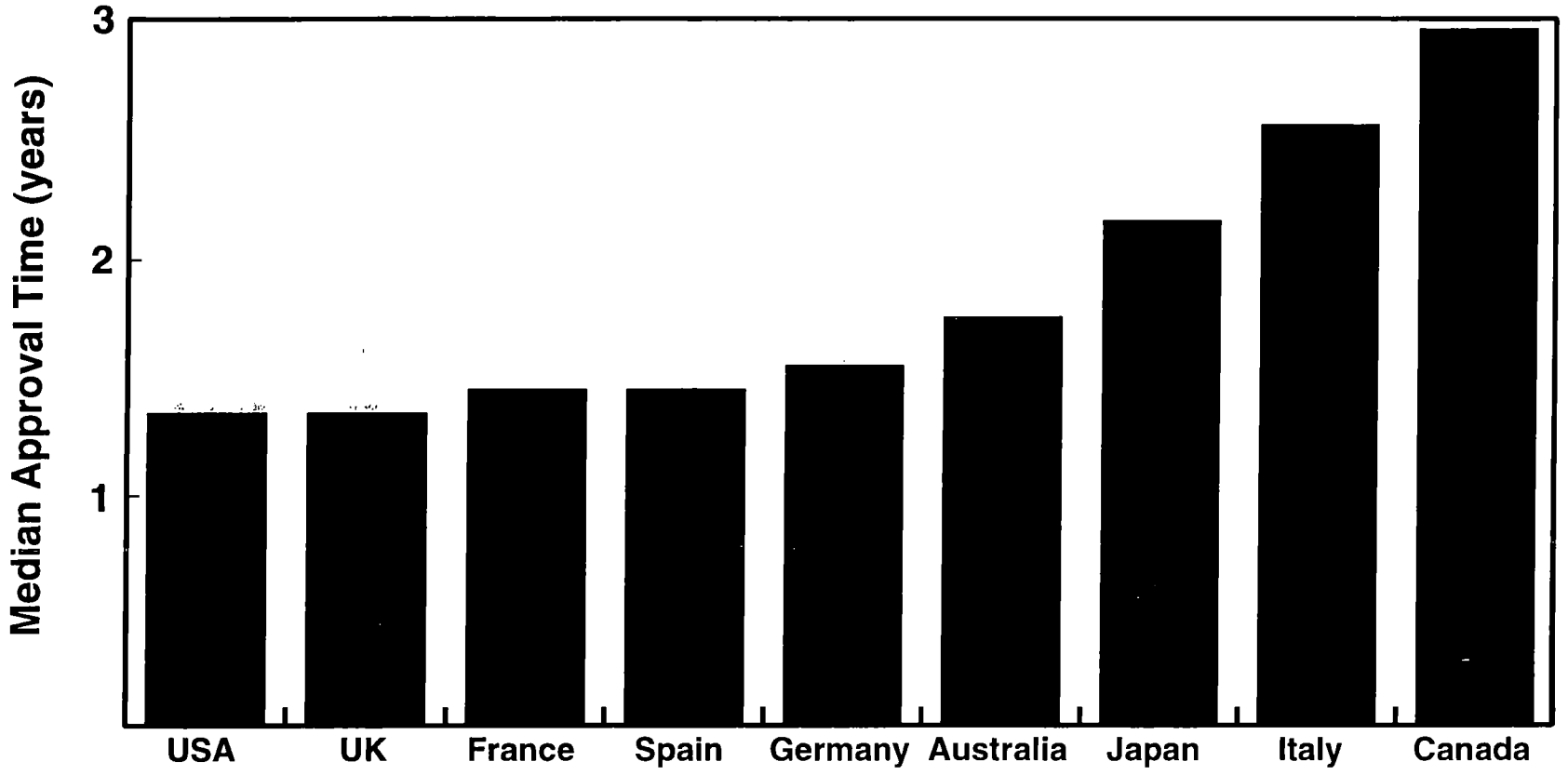
new cancer treatments. It responds to public interest in increased participation in the advisory committee process.

- **FEWER APPLICATIONS FOR ADDITIONAL USES OF APPROVED CANCER DRUGS**--Eliminating unnecessary FDA review of certain applications by physician-investigators to study unapproved uses for approved cancer drugs. In many circumstances, these additional applications are not needed. FDA will make clear that it does not require such submissions, therefore, researchers can devote more time to the challenges of cancer research.

IMPACT: Clinical research will be fostered by the relief of burdens associated with filing and maintaining additional applications; FDA will conserve resources that can be redirected to reviewing other applications for new therapies.

Median Approval Times for New Drugs Approved 1994-1995

(Preliminary data)



Source: Centre for Medicines Research, UK

Twelve Month Review*

New Drugs and Biologics

Actual 96% on time

Goal 55% on time

* If major amendment submitted late in the process, an additional three months is granted.

Public No Longer Confident Drug Supply Safe

- Private parties decide whether drugs are safe and whether they work, applying lower standards difficult for FDA to override. *(Section 7)*
- Decisions about whether a drug is safe or whether it works as expected based on less information. *(Section 4)*
- FDA no longer able to ensure public that drugs are being manufactured under safe conditions. *(Section 10)*
- Public may receive drugs that have been manufactured in some new way that makes them less safe or less effective. *(Section 13)*

Public No Longer Confident Drugs Actually Work

- Decisions about whether a drug works usually based on only one study. *(Section 5)*
- Drug companies able to promote new uses of their drugs even though those uses have not been shown to work or to be safe. *(Section 20)*
- Drugs approved for serious and life-threatening diseases even though adequate research has not been done to show that they work. *(Section 5)*
- Public could receive drugs for diseases with serious public health implications (e.g., sexually transmitted diseases) even though the drugs do not work nearly as well as those already on the market. *(Section 5)*

Safety of Blood and Human Tissue Supply Jeopardized

- **Blood facilities inspected by non-profit groups accredited by FDA but whose members are the blood manufacturers themselves.** ***(Section 26)***

- **FDA required to reconsider allowing a voluntary regulatory scheme for human tissue even though tissue infected with hepatitis B was imported into the U.S. and at least seven persons contracted HIV-1 from HIV infected human tissue while such voluntary standards were in place.** ***(Section 26)***

Public No Longer Confident Device Supply is Safe

- **Private parties decide whether devices are safe and whether they work, applying lower standards difficult for FDA to override.** ***(Section 11)***

- **Public using devices changed in a way that could affect whether they are safe or whether they work as expected even though those changes have never been seen or reviewed by FDA.** ***(Section 9)***

Public No Longer Sure Devices Actually Work

- **Public will be using devices approved on the basis of a lower standard of scientific evidence.** ***(Section 8)***

- **Device companies able to promote uses of devices not shown to be safe or to work.** ***(Section 18)***

Safety of the American Food Supply Jeopardized

- Private parties evaluate safety of food or color additives applying a lower safety standard difficult for FDA to override. *(Section 105)*
- Easier for cancer causing substances to be added to the food supply. *(Section 107)*
- States not able to impose requirements to ensure the safety of food in retail establishments, such as fast food restaurants. *(Section 108)*
- States severely limited in ability to require warnings to consumers about unsafe products, including foods. *(Section 108)*