

**ENSURING DRUG SAFETY:
WHERE DO WE GO FROM
HERE?**

HEARING
OF THE
**COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS**
UNITED STATES SENATE
ONE HUNDRED NINTH CONGRESS
FIRST SESSION
ON
EXAMINING THE FOOD AND DRUG ADMINISTRATION'S PROCESS OF
ENSURING DRUG SAFETY

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MARCH 3, 2005
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ENSURING DRUG SAFETY: WHERE DO WE GO FROM HERE?

THURSDAY, MARCH 3, 2005

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:02 a.m., in room 106, Dirksen Senate Office Building, Senator Enzi, chairman of the committee, presiding.

Present: Senators Enzi, Burr, Isakson, Kennedy, Murray, and Reed.

OPENING STATEMENT OF SENATOR ENZI

The CHAIRMAN. I will call the hearing to order. Good morning, and welcome to the second in a series on prescription drug safety.

On Tuesday we received a number of recommendations from the Food and Drug Administration and from outside experts on ways that the FDA can improve its process for weighing the benefits and risks of prescription drugs.

Today we are going to look to the future and consider the implications for drug safety, development and regulation. As I mentioned Tuesday, we have made major changes to the drug approval process over the past dozen years. Congress has passed a series of bills with overwhelming bipartisan support to bring more consistency, transparency and accountability to the drug approval process, but we have reached a critical juncture in the long history of the FDA. We need new and better ways to predict the safety and efficacy of the new drugs before they enter widespread use. We also need new and better ways to communicate with patients and physicians regarding the benefits and risks of new drugs. And we need the FDA, industry, physicians and patients to be vigilant and to work together to ensure the continued safety of prescription drugs once they are approved and on the market.

Doing nothing to address the current controversies is not an option. However, overreacting to recent events could be just as dangerous as doing nothing. With all due respect to the press, we should not be making policy to make headlines, or in response to the headlines. This issue is too important for that. We must take extraordinary care to find the right approach.

We have had and want to have the world's best example of drug safety. I have convened these hearings because I am concerned about the FDA and drug safety. All of us here today are aware of the recent controversies that have raised questions about the safety

of our prescription drugs and whether the FDA's process for reviewing and approving drugs is working.

Tuesday we heard about some of the immediate steps the FDA is taking to maintain the public's confidence in the Agency. We also heard about some steps that Congress may need to take. But as we consider how to deal with the questions raised by these recent controversies, we must also be focused on the future. As I said Tuesday, we should not sacrifice safety in order to speed drugs to the market, but we do not want to return to the days of the drug lag when desperate American patients waited for drugs that were available for months or even years in Europe, especially now that we stand on the cusp of tremendous medical advances based on new scientific insights.

Just in the past decade we have sequenced the human genome and doubled the NIH's budget. This has resulted in an explosion of basic scientific knowledge and the promise of an avalanche of new therapies. But despite that increase in scientific know-how many threatening diseases and conditions still lack effective treatment. More than a million Americans will have a heart attack this year. Some 600,000 Americans will suffer a stroke, and close to 500,000 women worldwide will die from breast cancer. The advances in biomedical knowledge have not been advanced by advances in new therapeutics. In fact the number of submissions to the FDA for new drugs and biologics each year has actually decreased since the completion of the human genome sequence.

Part of the problem is that science is racing far ahead of our current regulatory regime. For instance, most of the tools we use to test the toxicity of a drug are decades old. One-third of all drugs fail during preclinical or clinical trials due to the toxic nature of the compounds being tested. If we were better able to predict these failures before trials even began, we could both improve drug safety and save billions of dollars spent on research and development that leads nowhere. We need to match our investment in biomedical research through the NIH with new thinking, new methods and new resources to improve and streamline the regulatory process at the FDA.

But that raises three questions. First, how do we use new scientific knowledge to improve the medical product development process? Second, can we also use this knowledge to improve drug safety? And finally, how do we communicate new information about safety and risk more effectively within the Agency and to patients and to physicians?

I look forward to hearing the testimony of our witnesses. I trust they will be able to help us to begin to answer these questions. I know I speak for myself and Senator Kennedy when I say that the Nation is looking to us, the members of this committee, to ensure that drugs approved for use by the FDA are safe when used as intended, and do not pose an unreasonable risk to the public. And when we act to improve our drug approval system and to get the FDA ready for the future, we will act through this committee in a bipartisan and comprehensive fashion.

After Senator Kennedy makes his opening statement, we will hear from Dr. Janet Woodcock, the Acting Deputy Commissioner for Operations at FDA.

I will recognize Senator Kennedy for his statement.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. Thank you very much, Mr. Chairman, and I want to thank you and commend you for calling a second hearing on the safety of prescription drugs, and look forward to working with you to pass the legislation needed to correct the glaring drug safety problems identified in these hearings.

We learned a great deal on Tuesday's hearing about the problem. FDA obviously needs the authority from Congress to order drugs on the market to be relabeled when clear safety concerns arise. It is disgraceful it took nearly 2 years to relabel Vioxx after the so-called VIGOR trial. And Dr. Kweder of the FDA said such authority over relabeling would have helped, and that should be part of any legislation we propose.

We also know from Tuesday's hearing that FDA needs additional funds to monitor the safety of drugs on the market, and Congress needs to make room in the budget for this important priority.

Another major defect in the current law is that FDA lacks the authority to require manufacturers to conduct a further drug safety study after the drug has been approved and goes on the market. It is essential for FDA to be able to order such trials. Such authority may be the only way to ensure that the safety problems discovered after approval are studied effectively in clinical trials.

The problems of Vioxx and Celebrex were discovered in voluntary clinical trials to study potential new uses for the drugs after they first came on the market. Those trials showed conclusively that these drugs could cause heart attack or stroke in some patients. If Merck and Pfizer had not voluntarily conducted these studies millions might still be at risk from using these drugs. Most of the witnesses, including Dr. Kweder of FDA, said this additional authority would help the Agency respond to drug safety problems.

We have concerns about how FDA acts on drug safety issues. Although a warning was belatedly added to the Vioxx label as to cardiovascular risk, Dr. Kweder told us that the warning had little effect in encouraging safer use of drugs. We need to understand why.

Dr. Alistair Wood, who chaired the FDA's Advisory Committee meeting on Vioxx and related drugs, has said that the precaution was essentially meaningless. Some experts question whether relabeling is ever effective. FDA may well need better ways to encourage or even require safe use of drugs.

Still another issue is direct to consumer advertising, which encourages wide use of new drugs before we know enough about their safety. Vioxx and Celebrex were heavily promoted through direct consumer advertising. We have all seen the TV ads for these drugs with people skating and playing golf. These drugs were developed in the hope that they would reduce stomach bleeding, a risk faced by perhaps 5 percent of those who needed pain medications. Yet these ads did not say if you are at risk for stomach bleeding, this drug may be for you; ask your physician. Instead they peddled the drugs to everybody. A recent study found that large numbers of patients who used these drugs were not at risk for stomach bleeding. These ads almost certainly encouraged the unnecessary use of these drugs. Patients saw an ad, asked their doctor about them,

and started taking them even though another drug might have been just as effective. How many of these patients suffered a stroke or heart attack or died because of it?

Those drugs increase the risk of heart attack and stroke, perhaps doubling the risk. They were used widely by as many as 50 million people for more than 5 years before the risk was finally discovered. We will probably never know how many thousands suffered because of it. All prescription drugs carry some risk, and we are clearly not doing enough to minimize them. FDA needs better ways to do so, and I look forward to working with our chairman to enact more effective drug legislation.

Again I commend our chairman for his leadership, and I welcome our witnesses today and look forward to their testimony.

The CHAIRMAN. Thank you for your comment and insights. You add a lot of history to the committee.

I welcome our first witness which would be Janet Woodcock. Dr. Woodcock, the Acting Deputy Commissioner for Operations at the U.S. Food and Drug Administration. She has served as the Director of the Center for Drug Evaluation and Research at the FDA. The center is responsible for regulating prescription, over-the-counter and generic drugs. She has had close interactions with diverse constituencies including the clinical and scientific community, members of Congress, the administration, national media, patient and consumer advocacy groups, the international drug regulatory community, the pharmaceutical industry, and representatives of Federal and State agencies.

She was selected as the Director for CDER in 1994 and under her leadership the regulatory decisionmaking has been made more open and transparent to the public, and we congratulate you on your Acting Deputy Commissioner position now and look forward to your testimony, Dr. Woodcock.

STATEMENT OF JANET WOODCOCK, M.D., ACTING DEPUTY COMMISSIONER FOR OPERATIONS, U.S. FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Thank you. Mr. Chairman and distinguished members of the committee, I thank you for the opportunity to testify on the important issue of drug safety.

Five years ago this committee held hearings on adverse drug reactions. At that time the discussion focused on the estimated 100,000 deaths per year, as well as hundreds of thousands of hospitalizations and economic losses estimated in the billions of dollars. This is a longstanding and serious problem that I have worked on over many years of my professional life at FDA.

Since that hearing FDA has taken many important steps to enhance drug safety, but while drugs bring profound benefit to our population, we must continue to work together to mitigate their harm. Safety findings with antidepressants and the COX-2 inhibitors again illustrate how much more work needs to be done. FDA has taken additional steps as discussed at today's hearing to improve management and transparency around major drug safety issues.

Additional ideas for identifying drug side effects have been put forth by many parties. While these ideas are part of the solution,

you should know that they are not the whole answer. Why not? Because all drugs have side effects. Radically restricting drug availability would clearly reduce the number of side effects, but would also greatly diminish the treatments available to doctors and to patients.

Our long-term goal cannot simply be detection and restriction. It must focus on prevention and good management, and unlike the situation in 2000 there is now hope we can do just that, hope from new science and new technology.

What is this new science? Right now at the time a drug is approved, we know it works in some people and we know the safety results for those people. What we do not know is who it works in and who is at risk for a side effect, and we rarely know how to monitor people taking the drug to check if a side effect is developing and to intervene to prevent it.

Why is this? Not for lack of trying. By the time a drug is approved usually hundreds of millions of dollars have been spent on development and animal and human testing, but until recently we lacked the scientific tools to predict individual response to therapy. Today that is changing. New science such as pharmacogenomics, proteomics, advanced imaging technologies and computer modeling are making prediction possible.

FDA's Critical Path Initiative, launched last spring, is focused on modernizing the process for drug development to rapidly incorporate new scientific methods. These methods will help individualize therapy, select patients who will respond to treatment, and avoid people at high risk for side effects. This is not a futuristic dream. As I speak today, tests are being done in real patients in real medical practice to target therapy and avoid side effects.

In December FDA approved the first commercial pharmacogenetic test that allows patients and doctors to predict whether a person will be overdosed or underdosed by many common drugs. Once this test is done it is valid for a lifetime. So your relative, someone you know who may carry a gene that makes them metabolize drugs slowly and causes them to have many more adverse events from drugs, will know that they should start on lower doses.

And in the treatment of cancer, some targeted therapies are currently making a difference in people's lives. Many more are on the way. Targeting helps select people who have a good chance of a positive response to therapy. This improves safety because people who cannot respond do not get the drug.

As part of the Critical Path Initiative FDA will work to incorporate these new tools into drug development as rapidly as possible. For example, we will issue our final pharmacogenomic guidance very soon. This establishes processes for moving new scientific techniques into the drug development and regulatory process. Modernization will take time and scientific effort, but at the end of the day, having new tools to decide who should take a drug, who should not take a drug, and to monitor for side effects will bring about a new era in drug safety.

At the same time, new technology, information technology holds great promise for improving drug safety. With the help of electronic data linking medication use with health outcomes we can find rare

side effects that were not seen before approval. At the same time there are new ways to rapidly inform patients and prescribers about emerging safety data using electronic media. And equally important, computer-based interventions to provide support to prescribers has been repeatedly shown to reduce side effects and reduce hospitalization.

In summary, of course we must develop better ways to detect drug side effects, but detection is not enough. We must improve the science of therapeutics and make sure that that new information is in the hands of those who need it. These are the advances that will radically improve drug safety in this country.

Thank you.

The CHAIRMAN. Thank you. We always appreciate the additional information, and I want to assure you and all of the other people who will be testifying today that their entire statement will be made a part of the record.

In the way of questions, we heard the suggestion Tuesday that the FDA needs greater authority to require drug labeling changes. After hearing that I asked my staff if they would look to see what the present authority is. It says that if the labeling of such drug is false or misleading in any particular and it was not corrected within a reasonable time after receipt of written notice, that it can be pulled off the market by the FDA. That seemed to me to be quite a bit of authority. Is it sufficient authority?

I noticed with Vioxx that the timeline evidently began with discussions in October of 2001 and there was continued analysis and data from various studies, and then the FDA and Merck agreed to a new labeling on April of 2002. That is a six-month time span. Is that the amount of time that is usually required to make major labeling changes?

Dr. WOODCOCK. No, that is an unusually long amount of time. And actually the data from the VIGOR trial that we are talking about the safety data on Vioxx was available earlier than that. And currently with the recent changes that FDA has made in information dissemination we are now, as we announced several weeks ago, planning to put information directly out to the public on emerging safety issues. This will reach directly to the prescribers and the patients.

Part of the problem with label changes, even if a label change is made, that is a paper document. The old labels are in distribution and take a while to be changed over and so forth. So this new mechanism that FDA is proposing really should deal with this problem very effectively which is getting the information directly out to the people who need it in a timely manner.

The CHAIRMAN. Will there be negotiation before this data is put out to the public or is this just basic information, and then the labeling would change?

Dr. WOODCOCK. That is correct. What is proposed—and there is going to be time for public discussion of how this actually occurs—what is proposed is that FDA will put out the factual information about the finding before the label is actually changed.

The CHAIRMAN. Thank you. Tuesday we also talked about drug ads and how they need to be made clear, consistent and honest. Patients and physicians deserve to have as much information as pos-

sible about medical conditions and how to treat them, but the information also needs to be of high quality. Do you consider the current direct to consumer advertising to be high quality? Are there changes Congress or the FDA needs to consider making regarding regulation of these ads?

Dr. WOODCOCK. Clearly direct to consumer advertising is a double-edged sword. It has benefits in informing people about treatments that they may not have been aware for their condition. Our surveys show that doctors find that it improves and increases the amount of conversation they have with their patients about treatment options. On the other side though, it may, direct to consumer advertising in some cases may increase awareness of a drug, such as in the Vioxx situation, and people may not have a full understanding of the risks of that medication.

The direct to consumer advertising regulation takes into account the fact that patients must go to a physician to obtain a prescription for a drug, and so it is intended simply to allow that certain information be provided to the patient, but not complete information. The direct to consumer advertising is supposed to be balanced and not misleading. Those are the standards.

The CHAIRMAN. Thank you. Some have suggested that accelerating the drug approval through PDUFA has caused the FDA to decrease its focus on drug safety. Could you comment on this assessment?

Dr. WOODCOCK. The pre-market review, which is what is done under the PDUFA program, has about 50 percent of its focus on drug safety, and the use fee program enhanced that. To use a simple analogy, FDA is like the building inspectors. Someone else builds the building according to code. FDA does the code, writes the code, and then FDA comes in at the end and that is the review time under the user fee program, and we inspect the results and make sure they are up to code. What PDUFA did is help us add civil engineers or mechanical engineers. In our case it helped us add more scientific experts so that we could do that assessment quickly, and we could make sure that the standards for drug approval are kept up to date in current scientific standards.

So we feel there has been a tremendous focus on safety during the user fee years, and people have to recognize that the development of drugs, the clinical development, is done before the application is sent to FDA, and the PDUFA clock has to do with how long the FDA takes to review that information.

The CHAIRMAN. I want to thank you for your concise answers and great examples. My time has expired.

Senator Kennedy.

Senator KENNEDY. Thank you very much.

Just on the advertising issue, currently the manufacturer is allowed to flood the airways with ads for a drug on the day it is approved, and they can send salespersons to every doctor's office in the country to sway them to prescribe the new pill. It is hard to deny that the massive ad campaign led millions of patients who did not need them to take the COX-2 drugs, with tragic results.

I suppose the question that some of us would ask is, could this be happening with other drugs? Would it not be better to take a more cautious approach with advertising with newly approved

drugs, and do you think people are taking the medicines that are not suitable for them as a result of the ad campaign?

Dr. WOODCOCK. We have looked into how physicians treat direct to consumer advertising, their attitudes toward direct to consumer advertising. We asked them if they prescribe drugs that they would not have otherwise prescribed because the patients came in and asked for them. And in some cases that does happen. There is no doubt about it.

The construct that we are working under is that the physicians will be learned intermediaries and will decide after a conversation with the patient whether or not a particular drug is appropriate for that condition and that patient.

Senator KENNEDY. Have we gotten rid of these incentives? You mentioned the hearings that we had 5 years ago. I remember them, where we had all of these very incredible incentives to both the doctors and the ad people in terms of trips, tickets, just about everything under the sun. I was just wondering, just quickly, have those practices come back now or are we pretty free from all of those?

Dr. WOODCOCK. No, those practices are still going on, and I think most of us in the medical profession believe that the detailing and, for example, physicians on average have six visits per month of detail persons to their office. We believe that that has more influence on prescribing patterns than direct to consumer advertising, and certainly the budget is much larger.

Senator KENNEDY. I was thinking of the incentives that were given both to the doctors for the use of these drugs. You probably remember those hearings. As I say, I do not want to take a lot of time, but most of the abuses that we identified during that period of time, have they been dealt with pretty effectively or are some of them creeping back in. You can answer later on, whatever you want to do.

Dr. WOODCOCK. I will be happy to answer more fully later on, but I believe they still continue.

Senator KENNEDY. I would be interested if you could let us know, but I thank you.

On Tuesday Dr. Kweder acknowledged several FDA lapses in re-labeling and informing physicians about the risks of Vioxx. In your view what were the other mistakes or missed opportunities that resulted in the Vioxx drug disaster? Can you assure the American people that these kind of lapses will not happen again?

Dr. WOODCOCK. The lapses that we identified were the fact that a communication about the findings of the VIGOR trial were not effective in reaching the prescribers and the patients despite a label change that was made. For example, most prescribers really did not know about this finding, and so we are making much greater efforts now to communicate, as I said earlier, directly to prescribers and to patients so that they are aware of these findings. Everyone needs to recognize that today we know more about drug safety than ever before. One of the consequences of that is that we find out things that are bad. We find out more about adverse events of drugs.

A good example is the estrogens. A very large trial was done at NIH, and it was found that postmenopausal use of estrogens in-

crease several serious conditions including heart disease and breast cancer. This drug had been on the market for 45 years. It is not a cause for dismay that we are learning these things. It means that we are making medical progress and we finally have the means to understand these problems. What we need to do is move forward in that area and continue to learn more about drug side effects and how to avoid them.

Senator KENNEDY. I think it is a good thing to get that information out to the public as quickly as possible. At the Tuesday hearing we heard the FDA lacked the ability to require, not just to request, labeling changes to drugs already on the market. I am sure much of the public simply assumed that FDA had the basic authority to assure the safety of the medicines that they take. Maybe equally shocking for the public is to realize the FDA cannot require manufacturers to conduct follow-up safety studies on drugs already on the market. The Chairman pointed out that you have the power, you can withdraw it, so you have the heavy hand. But withdrawing a drug disregards the value that a particular drug, even I think the COX-2 drugs, would have for some patients on it, and withdrawal is a very dramatic step. Do you not think that relabeling authority would be helpful in avoiding safety problems and also do you not think FDA should be able to require safety studies of approved drugs if there is a public health need to do so?

Dr. WOODCOCK. I think there are tradeoffs there and I think that is something that has been debated a long time and that Congress will debate. I do believe the steps we have taken to have information directly from FDA to the public, to the practitioners and to the patients will help deal with some of these problems. If there is a need for an additional study to be done it is going to become quite apparent as we communicate this safety information.

Senator KENNEDY. My time is up, Mr. Chairman. Thank you.

The CHAIRMAN. Thank you.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

Welcome, Dr. Woodcock. It is great to see you. Thank you for what you do. Let me just ask you very plainly, can manufacturers go to market on a new drug that has been approved where the FDA has not agreed to the labeling on that original package?

Dr. WOODCOCK. No.

Senator BURR. So no product that is approved by the FDA can be placed on the market unless a manufacturer has had a sign-off by the FDA on the original labeling?

Dr. WOODCOCK. That is correct.

Senator BURR. I think individuals have suggested that either somebody hid something or the FDA's process is in fact broken. Do you believe that the FDA is approving dangerous drugs to go on the market today?

Dr. WOODCOCK. I believe on the basis of my professional experience, which is very extensive, and that my knowledge of approvals in past decades, we have the strongest and most detailed scientific evaluation of drugs that has ever occurred anywhere in the world today.

Senator BURR. So our approval process is not broken?

Dr. WOODCOCK. No. It is stronger than it has ever been.

Senator BURR. Can we all agree that it could get better?

Dr. WOODCOCK. It has got to get better.

Senator BURR. Can you tell me how many labels Vioxx has had?

Dr. WOODCOCK. No. [Laughter.]

Senator BURR. It was approved in May of 1999 I believe. I think with material changes, it is either two or three. I would ask the chairman for unanimous consent that the committee allow the labels that have been available for Vioxx to be included as part of the record, if I could get the chairman's attention for one second. [Laughter.] Mr. Chairman? Mr. Chairman, if I could get your attention for 1 minute, I would ask unanimous consent that the labels that Vioxx has carried on its packaging since May of 1999 be included as part of the record.

The CHAIRMAN. Without objection.

Senator BURR. Thank you.

[The Vioxx labels follow:]

[Editors Note—Due to the high cost of printing, previously published materials submitted by witnesses may be found in the files of the committee.]

Senator BURR. I think it is important because it is my understanding that the original labeling for Vioxx included under adverse events heart attack, stroke, congestive heart failure, high blood pressure. It was not black-boxed, it was not something that was emphasized, but it was an indication that had been discovered in the clinical trials. Is that your understanding?

Dr. WOODCOCK. I do not know about myocardial infarction of heart attack. These other ones that you mention are true for all the anti-inflammatory agents.

Senator BURR. So there is a common thread that runs through these and one would expect physicians to be fairly well aware of that.

Dr. WOODCOCK. Most are.

Senator BURR. Let me ask you, there are some that suggest, I think all suggest we need a more robust postapproval surveillance process. Some suggest that that has to be outside of the FDA. Can I ask you for your professional opinion on whether it needs to be inside the FDA or outside the FDA first?

Dr. WOODCOCK. There are two issues. One issue is a robust surveillance system, and that means more active surveillance, better access to the data that is out there about the use of drugs in this country. That needs to be enhanced. It does not need I think to be one place or another. It needs to be enhanced.

Senator BURR. Let me stop you there if I could because I want you to clarify another thing for the committee. Some have suggested that the clinical data should be made available not just to the physician world, but to the general public. In your professional opinion do you believe that the general public can disseminate clinical data in a way that it would be useful to their decision process?

Dr. WOODCOCK. Can you clarify which clinical data you are referring to?

Senator BURR. It would be the clinical trials.

Dr. WOODCOCK. We have highly-trained scientists. We have to train—and they have all gone to medical school or gotten their PhD's—we have to train them additionally once they arrive at the

FDA to analyze the raw data on clinical trials, and we are extremely expert at that, but we can always improve.

That said, it is not something that the general public really could evaluate. Before we had electronic data we would get this in a tractor-trailer coming to the FDA. It is a very large amount of data that is involved. We have already said we believe summaries of information and results should be made available to the public.

Senator BURR. If you could finish the answer that I interrupted you on.

Dr. WOODCOCK. Yes. As far as who should make decisions around drug safety, that is the second part. First we need a strong surveillance system in this country. Then the question is who makes the decisions. Some people have said they believe that members of the FDA who were involved in the decisionmaking have some sort of bias, an intellectual bias or whatever against removing the drug. For that reason FDA has proposed that we put together a board composed of qualified experts from both within the FDA and external, none of whom would have been involved in the decision to approve that drug, to address that specific issue.

But in general, in my professional opinion, it is very important to have people involved in decisionmaking who actually treat patients with that condition, because if you only look at risk we would not have any drugs. It would not be sensible to have any drugs because they all cause harm. Even acetaminophen very common drug, over-the-counter, number one cause of drug-induced liver failure in the United States. If you took that fact in isolation what you would say is that should not be on the market. So you have to have the benefit side right in front of you when you are evaluating the safety problems of drugs.

Senator BURR. My time has run out, but you do uphold the FDA's proposal that that be housed within the FDA but with outside individuals, outside experts, outside docs coming in and participating in the review process?

Dr. WOODCOCK. That is correct.

Senator BURR. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Burr.

Senator Murray.

Senator MURRAY. I believe Senator Reed was ahead of me.

The CHAIRMAN. Oh, I am sorry. Senator Reed?

Senator REED. Thank you, Mr. Chairman.

Thank you, doctor, for your testimony. Let me continue a point that Senator Burr raised, the issue of two standards that you have to apply when reviewing a drug: safety and efficacy, and also the standard of risk benefit analysis. Those standards seem in some cases contradictory or at least have to be balanced. Can you elaborate on how you are doing that in a practical situation?

Dr. WOODCOCK. The FDA is charged with making sure that drugs on the market are safe and effective. We interpret that safety to mean that the benefits of the drug in the intended population outweigh its risk, because there is really no way that we can approve drugs that are absolutely without risk. So when we say drugs are effective and safe, we mean that their proven demonstrated

benefits from the clinical trials outweigh the risks of the drug for the people that it is indicated for.

Senator REED. Has that always been the regulatory standard or is this something that had evolved over the last several years. Has there been any recent change that we should note here?

Dr. WOODCOCK. That has always been the regulatory standard. The change over the past decades is now drugs are studied in more people before they are put on the market, and we know more about them.

Senator REED. Let me turn to another topic, clinical trials. We acknowledge that every drug goes on the market with a clinical trial, but I think we also acknowledge that all clinical trials are not equal. Some are testing the best hypotheses, some might not have the best hypotheses. Some might have a long longitudinal survey. Some might be very quick. Practically speaking, I think you would acknowledge that there are differences in clinical trials. How do you deal with different kinds of trials in terms of making a decision about putting a drug on the market?

Dr. WOODCOCK. That is a good question, and I used earlier the analogy of the building inspectors and the building code. Not only does FDA do the building inspection, we look at the results at the end, we write the code, so we say what the standards are for showing safety and what the standards in the clinical trials would be for showing effectiveness. So we would say, "You have to test these patients in this manner for 3 months, 6 months, whatever we say, and show these endpoints for effectiveness, and you have to do it twice. You have to replicate the results in another trial." So we set those standards and then when we are doing the review, we are reviewing against the standards that have been established.

Senator REED. And there is a constant process of evaluating how good you are in setting these standards internally.

Dr. WOODCOCK. Yes. We try to revise our guidance as we learn from things that have gone wrong, from things that have gone right in the clinical trials and post marketing.

Senator REED. Without elaborating in detail on the latest situation with Vioxx, have you reevaluated the standards you set and the trial dynamics that you put in place?

Dr. WOODCOCK. Yes. When we discussed with our advisory committee a couple weeks ago, one of the issues that was raised is that drugs that are intended to treat symptomatic conditions, say arthritis, typically if they are just for symptoms, those drugs have not been studied for a long time in the clinical trials, 3 months, 5 months, something like that. That has increased over time. In other words we require much more study than we used to 10 years ago, 15 years ago. Nevertheless it was clear that there probably, even though Vioxx and Celebrex had more patients than any other anti-inflammatory drug had had before they got on the market, it still was not enough people and enough time to detect these particular problems. So we have to continue to evaluate how to deal with that.

Senator REED. A final question since I have very little time left. That is, we have passed the PDUFA bill. We have passed the FDA Modernization Act. Part of that is to streamline the delivery of drugs to the marketplace, but inherent in that is at least the issue

of whether or not the streamlining has curtailed clinical trials, curtailed judgment about putting drugs in the marketplace. Very, very briefly, what is your conclusion?

Dr. WOODCOCK. Well, again, I think that you have to separate the time and the standards for doing the clinical trials which occurs before they are sent to FDA from what is the subject of the user fee legislation which has to do with how fast the FDA reviews those results once they are in house. What the user fee program has also given us is more experts who can work on setting the standards during the clinical trials, and although we have not advanced as much as I would like in the clinical outcome area, we have made tremendous advances in clinical pharmacology in many of the underlying specialties, and these have improved drug safety quite a bit.

Senator REED. Is it fair to say that these legislative initiatives have basically changed the response of FDA, but not the requirements of the investigators to pursue these investigations, and has not materially in your view affected the standards for clinical trials or for evaluation?

Dr. WOODCOCK. No. I think the clinical standards have remained the same. There have been many additional safety standards added over the past decade as we have learned more. You can ask the pharmaceutical companies about this because they are constantly saying, look, you now have to test electrophysiologic parameters for the heart and certain other types of drug metabolism and so forth. So these things have been added. The overall standards have not been lowered, but we can review drugs faster because we have more experts.

Senator REED. Thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman. I really appreciate your having these hearings. I think it is really giving us some good insight and information and will help us move forward to some possible legislative solutions.

I do want to recognize a witness from the second panel who is with us from the University of Washington, Dr. Bruce Psaty. He is a professor of medicine, epidemiology and health services at the University of Washington, and I appreciate him traveling all the way out here to participate.

Let me just begin, Dr. Woodcock, with we have heard a lot about the FDA approval process and the potential conflict of interest that may be there because of the PDUFA fee. Can you tell us if you can the number of new drug applications and the number of new drugs that have been approved versus how many have been disapproved?

Dr. WOODCOCK. I cannot tell you the numbers out of my head.

Senator MURRAY. Percentage perhaps?

Dr. WOODCOCK. Traditionally I think about 25 to 30 percent are not approved. I do not believe that number has changed much over time, over the decades.

Senator MURRAY. So even with the PDUFA fee, the number disapproved is about the same percentage.

Dr. WOODCOCK. I would like to say though that although that means perhaps we have not decreased our standards, it is a failure

of the enterprise. Those 20 percent of drugs that are turned down, many patients were exposed to those drugs during development and gave their time and effort to trying to see whether they were safe and effective. We need to do better on prediction. That is not a good number really.

Senator MURRAY. What is the average length of time for new drug approval today?

Dr. WOODCOCK. For priority drugs that are felt to bring a public health advance or an advance in therapy of some kind, it is about 6 months for FDA to review those, and for the standard drugs it is about 13.

Senator MURRAY. About 13 months, okay. I want to follow up on what Senator Reed was asking you about in terms of clinical trials and working with the manufacturers. Do you work with them to make sure that they are not just focusing on whether a drug is effective or whether or not there are risks attached to that drug?

Dr. WOODCOCK. One of the innovations in the user fee program, which I support highly, is greater interaction of the regulators with the drug companies while they are doing the clinical, the human experimentation phase. What we do, we tell them we are going to expect, say, you to have 500 patients exposed for this amount of time, and we would expect you to do these kind of safety tests during the clinical trials. So there is an opportunity for the FDA to intervene and explain its expectations on safety and effectiveness during the trials.

Senator MURRAY. So you are not just looking at whether the drug is effective, you are working with them to make sure that we are looking at risks?

Dr. WOODCOCK. We just did an internal survey of how much effort we spend on safety versus effectiveness, and we found for the whole center we spend 50 percent of our time on safety.

Senator MURRAY. You were also asked by Senator Burr about this independent office on drug safety. I think you answered him that you did not think it was necessary. I would like to ask a few questions about that. Are the same FDA employees reviewing the new drug applications and the postmarket adverse events data, do you know?

Dr. WOODCOCK. Not the data. The way the structure is set up, the Office of New Drugs continues to follow a drug throughout its life cycle until it becomes generic, in which case the Officer of Generic Drugs takes over some of that. The postmarketing surveillance system which gets our MedWatch information, which is called our Ayres database, is operated by the Office of Drug Safety. They run the surveillance system, and so they are looking at that data as it comes in.

Senator MURRAY. So the manufacturer is not working with the same employee throughout the entire—

Dr. WOODCOCK. Not necessarily on the MedWatch data, but they are working with the same division on their label all the way through the life cycle of the drug.

Senator MURRAY. What kind of processes do you have in place to protect against any conflict of interest?

Dr. WOODCOCK. We have a team approach to review. We have a large number of individuals who are involved in a hierarchical ap-

proach to review so that supervisors also look at the work of the primary reviewers, and that is all brought together in a team process.

Senator MURRAY. Is there a concern about conflict of interest or do you feel that you have enough employees?

Dr. WOODCOCK. The individuals reviewing all this information are physicians. They are at the Agency rather than out in private practice or industry because of their public health orientation. And there may be a concern about this intellectual bias because people were involved in approving a drug, and that is what I have heard.

Whenever we have a serious drug safety issue, more people are involved in looking at that, people who had no involvement in the pre-market decision. And the new procedures that have been put in place will even open up that more. So that should take care, in my mind, of the issue of is there some bias by those who were actually involved in the beginning.

Senator MURRAY. What would the drawbacks be of having an independent office?

Dr. WOODCOCK. Can you define "independent?"

Senator MURRAY. As I am hearing it defined by people who are suggesting it, separate from FDA looking at the post market.

Dr. WOODCOCK. I think people do not understand totally the drug life cycle. Medications are often approved for very narrow indications. The FDA remains involved as new trials are done. Say, cancer drugs, they are often approved for the most desperate cases, and then additional trials are done to see what the real use of that cancer drug would be in the wider population. Pediatric trials are done and so forth. So all the time after the drug has been approved, there is a very active process going on with new indications being added, new warnings. It is really a continuum before the pre-market and the postmarket. It is by no means that we sort of forget this drug after it is approved.

So you need the input of all the experts on the drug and the tremendous amount of expertise they have gained about that drug and maybe that class of drugs before marketing, in the postmarket period as well.

Senator MURRAY. I appreciate that very much. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Isakson.

Senator ISAKSON. Thank you, Mr. Chairman.

I apologize that I am late and did not hear your testimony and might be redundant in my questions, so be very brief or tell me I am redundant and to look it up in the book.

I think following up on the previous question, your opinion on this external review, just real quickly, what is your take on that or the need for it?

Dr. WOODCOCK. I think of course the FDA is open to various approaches and suggestions, but people need to have the correct—say in medicine you have to have the correct diagnosis before you move into treatment. I think people really need to think about what problem are they trying to address before thinking about what treatment to apply.

As I was just saying, the postapproval phase for a drug is a very active one where more clinical trials are going on, the label is being changed, the drug is being studied in additional populations. So the involvement of the medical team in the drug also continues throughout that time, and generally these are subspecialists. We have neurosurgeons, neurologists, gastroenterologists and so forth all across the medical subspecialties. They have very deep and profound knowledge of their particular area and the use of therapeutics in that area.

So it would be difficult to imagine moving that process to some other unit, but perhaps people mean something else by what they are saying with the independent safety board.

Senator ISAKSON. So within FDA following the approval of a drug there is an ongoing tracking of the effects of that—or any effects that are reported by physicians prescribing that drug, and that comes to FDA?

Dr. WOODCOCK. Yes. That part comes to the Office of Drug Safety, but all the clinical trials and oversight of those clinical trials and the safety of the subjects and how the trials are designed and so forth, those are done by the medical divisions.

Senator ISAKSON. How does that come back to FDA, that information, on paper and pencil or—

Dr. WOODCOCK. It is normally electronic, and these additional studies have to be done under an IND because human subjects are being exposed in experimental conditions. So the FDA has a great deal of interaction and oversight into those ongoing trials.

Senator ISAKSON. Are you one that subscribes to a belief that I am coming to believe, and that is, one of the greatest things we could do in health care overall is get technology involved so this information flows seamlessly and accurately from physician and pharmacist and patient, and there is an integration of that information so it can be pulled out quickly?

Dr. WOODCOCK. You are reflecting my testimony. I totally agree with that, and we have been working very hard at the FDA to do our part to make that happen.

Senator ISAKSON. Are you familiar with a company by the name of Greenway?

Dr. WOODCOCK. No.

Senator ISAKSON. After the hearing I will give you a note. There is some development on that end that is now actually out in practice in my home State of Georgia that is showing great promise in terms of information technology, patient, doctor, pharmacist.

Last I just have a comment. You all take a lot of knocks lately and there has been a lot of criticism. I would like to just tell a story for the sake of the chairman and the committee. On the 12th of September in 2001 a pharmaceutical company in my district contacted me, Solvay. They had a burn treatment known as Flamazine, which was in its final—I do not know if I am using the right word but I remember they kept using the word “protocol”—before issuance. New York City had run out of the only other approved ointment of this type, and obviously we had a serious, tragic—I just want everybody to know that FDA’s response that day and the ability to get those badly-needed medicines to New York City in a time of great crisis was nothing short of unbelievable,

which I do not think portends that you only do timely work in an emergency, I might add, but you do good work all the time. I appreciate what you do.

That is all of my questions and comments, Mr. Chairman.

The CHAIRMAN. Thank you. That reminds me that I refer to this hearing room as the reassurance room. Following September 11th, while most of the Senators were up in New York looking at Ground Zero, those of us in the Banking Committee were in this room holding hearings with the stock market people to reassure America that the stock market was still working, that it would open on the following Monday, and that everything would be fine, and that there was plenty of backup.

Part of what we are doing with these hearings is giving some reassurance on the condition of FDA in getting their insight and others' insights into the kinds of things we can do to do the job even better.

I thank you very much for your testimony. We will keep the record open for another 10 days. That will give you a chance if you want to expand on anything that you have answered today, and Senator Kennedy had one particularly difficult one to answer just on the spur of the moment in the timeframe that we have, and also give members of the panel an opportunity to address additional questions that may be more technical than the general public might be interested in, but that would be helpful to our decisions. Thank you very much for testifying today.

[The joint prepared statement of Dr. Woodcock and Dr. Kweder follows:]

JOINT PREPARED STATEMENT OF DR. WOODCOCK AND DR. KWEDER

INTRODUCTION

Mr. Chairman and members of the committee, I am Dr. Sandra Kweder, Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss drug safety and the drug approval process.

Because of the importance of these issues, you are holding two hearings over the course of 3 days. Dr. Janet Woodcock, FDA's Acting Deputy Commissioner for Operations, will appear at your hearing on March 3. We have one written statement to address both hearings.

SAFETY IS A HIGH PRIORITY

Let me begin with a few words about safety, and I will return to this issue throughout our written testimony. Modern drugs provide unmistakable and significant health benefits. FDA's drug review process is recognized worldwide as a gold standard. Indeed, we believe that FDA maintains the highest standards for drug approval. There have been significant additions to those standards during the last several decades, in response to advances in medical science. Currently, FDA approves drugs after they are studied in many more patients and undergo more detailed safety evaluation than ever before. FDA grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy. However, no amount of study before marketing will ever elucidate all the information about effectiveness or all the risks of a new drug. Therefore, post-marketing surveillance is extremely important.

Adverse effects that are not detected during clinical trials are identified after approval through post-marketing clinical trials, spontaneous reporting of adverse events, or observational studies based on more widespread use of the product following approval. That is why Congress has supported and FDA has created a post-market drug safety program designed to collect and assess adverse events identified after approval for all drugs we regulate.

This program serves as a complement to the pre-market safety reviews required for approval of prescription drugs in the U.S. FDA also evaluates and responds to adverse events identified in ongoing, post-market clinical trials that test approved drugs for other indications. We also evaluate and respond to events reported by physicians, their patients, or drug manufacturers. With this information, we make label changes and take other regulatory action as needed.

It is important to emphasize that all approved drugs pose some level of risk, such as the risks identified in clinical trials and listed on the labeling of the product. Unless a new drug's demonstrated benefit outweighs its known risks for its intended population, FDA will not approve the drug. However, we cannot anticipate all possible effects of a drug based on data from the clinical trials that precede approval.

NEW FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

November 2004 Five-Step Plan

At FDA, we are constantly striving to improve our processes and methods, and thereby better serve the public health. Recent developments have prompted us to refocus our drug safety efforts and take additional steps to identify drugs that may have unacceptable risk profiles.

On November 5, 2004, Acting Commissioner Crawford announced a five-step plan to strengthen FDA's drug safety program. First, it called for FDA to sponsor an Institute of Medicine (IOM) study to evaluate the current drug safety system. An IOM committee will study the effectiveness of the U.S. drug safety system, with an emphasis on the post-marketing phase, and assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used. We will ask IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

Second, Dr. Crawford announced that CDER would implement a program for addressing differences of professional opinion. I am pleased to report that CDER recently put this program into effect. Currently, in most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisers, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact.

In an effort to improve the current process, CDER has formalized a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed and transparent in its decision-making process. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER will conduct a national search to fill the currently vacant position of Director of the Office of Drug Safety (ODS), which is responsible for overseeing the post-marketing safety program for all drugs. CDER is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and surveillance, and a strong commitment to protecting the public health. CDER is working with the Office of Personnel Management on this search.

Fourth, in the coming year CDER will conduct additional workshops and advisory committee meetings to discuss complex drug safety and risk management issues. Most recently, for example, the Agency conducted a 3 day Advisory Committee meeting that examined COX-2 selective non-steroidal anti-inflammatory drugs and related medicines. The committee held its meeting on February 16-18, 2005, and heard presentations from more than 25 experts. At the end of the meeting, the Advisory Committee issued recommendations that the Agency is promptly and carefully reviewing before taking further action.

Finally, FDA intends to publish final versions of three guidances that the Agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances should assist pharmaceutical firms identify and assess potential safety risks not only before a drug reaches the market but also after a drug is already on the market. FDA expects to publish the final guidances in the second quarter of 2005.

February 2005 Drug Safety Announcement

On February 15, 2005, HHS Secretary Leavitt and Acting Commissioner Crawford unveiled a new, emboldened vision for FDA that will promote a culture of openness and enhanced oversight within the Agency. As part of this vision, FDA will create

a new independent Drug Safety Oversight Board (DSB) to oversee the management of drug safety issues, and will improve transparency by providing emerging information to health providers and patients about the risks and benefits of medicines.

Under this proposal, FDA will enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety by creating an independent DSB. The DSB will oversee the management of important drug safety issues within CDER. The DSB will be comprised of individuals from FDA who were not involved in the initial review of the drug, as well as medical experts from other HHS agencies and government departments (e.g., the National Institutes of Health and Department of Veterans Affairs). CDER's Deputy Director will serve as the Chair of the DSB. The DSB also will consult with other medical experts and representatives of patient and consumer groups.

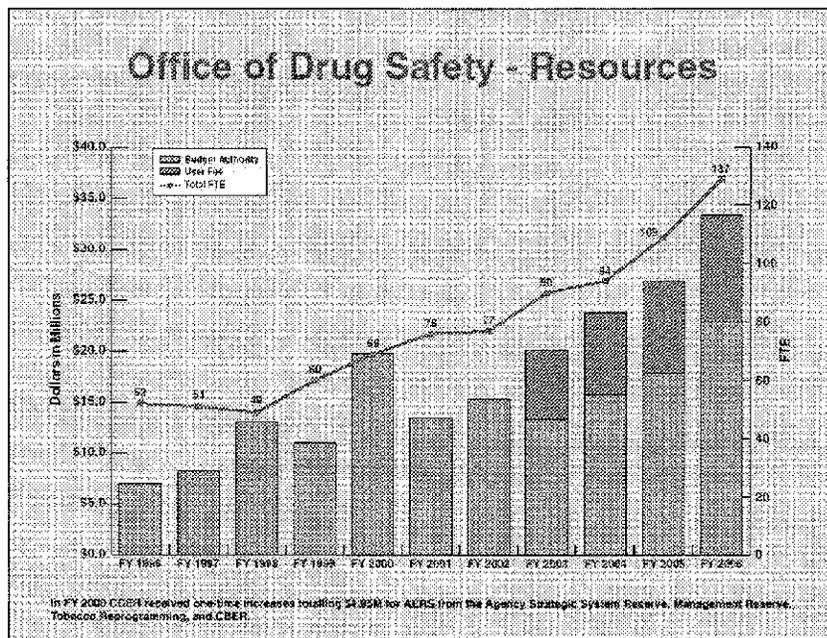
FDA will also increase the transparency of the Agency's decision-making process by establishing new and expanding existing communication channels to provide drug safety information to the public. These channels will help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their health care professionals to make better-informed decisions about individual treatment options. The Agency is also proposing a new *Drug Watch* web page that will include emerging information about possible serious side effects or other safety risks for previously and newly approved drugs. This resource will contain valuable information that may alter the benefit/risk analysis for a drug or affect patient selection or monitoring decisions. The web resource may also contain information about measures that patients and practitioners can take to prevent or mitigate harm. This information resource will significantly enhance public knowledge and understanding of safety issues by discussing emerging or potential safety problems even before FDA has reached a conclusion that would prompt a regulatory action. As always, FDA is committed to maintaining patient privacy as it implements these measures.

As FDA develops these communication formats, the Agency will solicit public input on how FDA should manage potential concerns associated with disseminating emerging information prior to regulatory action. The Agency will also issue draft guidance on procedures and criteria we will use to identify drugs and information that will appear on the *Drug Watch* web page. In addition, FDA will actively seek feedback from health care professionals, patients and consumers on how best to make this information available to them.

Increased Funding for the Office of Drug Safety

FDA has a longstanding commitment to provide a strong resource base for ODS. As the graph set forth below demonstrates, we have steadily increased the financial and human resources dedicated to post-market drug safety over the past decade.

The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. The Administration's proposed budget for ODS will increase by \$6.5 million, including \$1.5 million in user fees, for a total fiscal year 2006 ODS funding level of \$33.4 million. PDUFA resources will represent nearly one-third of the ODS budget for the coming year. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.



THE DRUG APPROVAL PROCESS

Pre-Approval Focus on Safety

FDA's focus on safety begins at the earliest stages of drug development, when we review a product under an investigational new drug (IND) application. During the IND period, products must complete three phases of clinical (human) trials. Phase I studies involve the initial introduction of an IND drug into humans to assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. However, before beginning human trials, the sponsor must perform extensive animal toxicity studies. Researchers closely monitor these studies. They may conduct Phase I trials in patients, but often rely on healthy volunteer subjects. In general, these studies yield initial safety data and useful information to establish the appropriate dose of the drug.

Phase II includes the early controlled clinical studies conducted to obtain additional information on appropriate dosing, as well as preliminary data on the effectiveness of the drug for a specific indication in patients with the disease or condition. This phase of testing also helps identify short-term side effects and risks possibly associated with the drug. Phase II studies are typically well controlled, closely monitored and conducted in studies that usually involve several hundred patients. In these studies, researchers compare results of patients receiving the drug with those who receive a placebo, a different dose of the test drug, and/or another active drug. At the conclusion of these studies, FDA and the sponsor meet to determine if the drug's development should advance to Phase III and how to design and conduct further trials.

Finally, researchers design Phase III trials for a larger number of patients and build on the data gained from the first two phases of trials. These studies provide the additional information about safety and effectiveness needed to evaluate the overall benefit-risk relationship of the drug. Phase III studies also provide the basis for extrapolating the results to the general population and provide essential information for the package labeling. Once the results of all the clinical trials are available, the sponsor of the application (usually the manufacturer of the product) analyzes all the data and submits a new drug application (NDA) or biologics license application to FDA for review.

Post-Approval Risk Assessment

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA on their drug. Also during this period, we continuously receive adverse event reports through our MedWatch system from other sources such as health care providers and patients. Safety experts review and analyze the reports to establish the frequency and seriousness of the adverse events. Our response to information from this ongoing surveillance depends on an evaluation of the aggregate public health benefit of the product compared to its evolving risk profile. FDA carefully considers the seriousness and the frequency of reported adverse events as well as the estimated number of patients who benefit from the drug. The occurrence of a rare event, even a serious event, may or may not, by itself, be sufficient to take a drug product off the market. Adverse event reports do not solely provide all the data necessary to identify any potential risks that may be associated with a specific product or class of products; however, over time, they provide us with another piece to a complex puzzle.

If the public health benefit of the product outweighs its known risks for the intended population and intended use, FDA allows the continued marketing of the drug. Often, as more becomes known about the potential risks or benefits of a product, its label will be revised so that it better reflects information on appropriate use. For example, FDA may ask the manufacturer to revise the labeling to add information on adverse reactions not previously listed, to add new warnings describing conditions under which the drug should not be used, or to add new precautions advising doctors of measures to minimize risk. FDA often issues Public Health Advisories and information sheets for health care providers and patients that discuss the new safety information. In the event of reports of death or life-threatening injury, FDA and the sponsor may consider restricting the distribution of the product or removing it from the market. Our action will depend on the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a benefit, the availability of alternative therapy, and the consequences of not treating the disease.

The issue of how to detect and limit adverse reactions can be challenging. How to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health is multifaceted and complex, and involves scientific as well as public health issues.

STATUTORY CHANGES TO DRUG APPROVAL AT FDA

FDA was founded in response to concerns about safety, and attention to safety pervades everything that we do. In the Federal Food, Drug and Cosmetic Act of 1938, Congress gave FDA the authority to review the evidence that a drug was safe for its intended use. In 1962, Congress added a requirement that drug sponsors also demonstrate that a drug is effective, using adequate and well controlled studies. Thus, drug safety means that the demonstrated benefits of a drug outweigh its known and potential risks for the intended population and use. In recent years, Congress has enacted legislation that provides significant additional tools to improve our focus on safety: the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Modernization Act (FDAMA).

In 1992, Congress enacted PDUFA. This landmark legislation provided significant resources for FDA to hire more medical and scientific reviewers to conduct pre-market reviews, to hire support personnel and field investigators to speed the application review process for human drug and biological products, and to acquire critical information technology infrastructure to support our review process.

In 1997, following the success of PDUFA I, Congress reauthorized the program for an additional 5 years when it enacted FDAMA of 1997. With PDUFA II came higher expectations for product reviews and additional goals designed to reduce drug development times.

In 2002, Congress reauthorized PDUFA for a third time. PDUFA III places great emphasis on ensuring that user fees provide a sound financial footing for FDA's new drug and biologic review process and, for the first time, gives FDA authority to expend PDUFA resources on risk management and drug safety activities during the approval process and during the first 2 to 3 years following drug approval. Mr. Chairman, your Committee played a significant role in creating and reauthorizing PDUFA, and on behalf of my colleagues at FDA and countless patients throughout America who benefit from the therapies approved under the PDUFA process, I thank you for your efforts.

One of the primary goals of PDUFA was to address the significant delay in U.S. patients' access to new medicines. The objective was to increase benefits to patients, without increasing risks. Before PDUFA, drug lag was a serious concern for U.S.

patients and practitioners. Life-saving drugs were available to patients in other countries months and sometimes years before they were available in the U.S. Because of the additional resources and process improvements implemented since PDUFA I became law, the average FDA drug review time has declined by more than 12 months.

It is important to emphasize that a recent study by Berndt, et al. of the National Bureau of Economic Research found no significant differences in the rates of safety withdrawals for drugs approved before PDUFA compared to drugs approved during the PDUFA era. This research confirms FDA's analysis on the same subject. In addition, we are now adding black box warnings sooner than we did before PDUFA. This indicates that PDUFA has been successful in both speeding access and preserving safety.

In general, PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a sponsor seeks FDA approval for a new drug or biologic product, it must submit an application accompanied by a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Before PDUFA, taxpayers alone paid for product reviews through budgets provided by Congress. Under the PDUFA approach, industry provides additional funding in return for FDA's efforts to meet drug-review performance goals that emphasize timelines but do not alter or compromise our commitment to ensuring that drugs are safe and effective before they are approved for marketing.

PDUFA III—GREATER EMPHASIS ON DRUG SAFETY

PDUFA fees are essential to our efforts to improve drug safety. Our trained health professionals work to help ensure and improve drug safety using a process of scientific review, monitoring, and analysis throughout the life cycle of the drugs we approve for marketing. A focus on safety initiates during the pre-marketing phase, when the earliest work on drug discovery begins. As the drug development process continues, we evaluate the safety of the therapeutic compound over a number of years during pre-clinical testing, clinical trials involving humans and eventually, with the submission of an NDA for FDA review. Thanks to PDUFA, we are able to commit far greater resources to our important safety responsibilities.

Under PDUFA III, Congress granted authority for FDA to expend user fees for post-market safety review. FDA made this a top priority during our PDUFA negotiations. Beginning with PDUFA III, for drugs approved after October 1, 2002, we can spend PDUFA resources on "collecting, developing, and reviewing safety information on drugs, including adverse event reports" for up to 3 years after the date of approval. The initiative to address drug safety for PDUFA III products helps FDA better understand a drug's risk profile, provide risk feedback to the sponsors and provide essential safety information to patients and health practitioners.

From October 1, 2002, through December 31, 2004, FDA reviewed 63 risk management plans for drug and biologic products. Twenty-eight of these related to applications submitted after PDUFA III took effect. We also conducted pre-approval safety conferences, risk management plan reviews, drug safety meetings, and meetings with sponsors to discuss proposed drug supplements.

In response to PDUFA III, FDA held a public meeting in April 2003 to discuss risk assessment, risk management, and pharmacovigilance practices. On May 5, 2004, based on the valuable information generated through the meeting process, we published three draft guidances on these important drug safety topics. FDA received extensive comments on these documents, and we expect to publish all three final guidances in the second quarter of 2005.

SAFETY ADVANCES IN FDAMA

Enacted in 1997, FDAMA has been an important addition to FDA's legal framework. FDAMA passed following a thorough Congressional examination of the Agency's policies and programs. It instituted a number of comprehensive changes, reaffirmed the Agency's vital role in protecting the public health and served as the vehicle for enacting PDUFA II.

Pediatric Exclusivity and Safer Use of Drugs in Children

For decades, children were prescribed medications that had not been studied for safety and efficacy in pediatric populations. As a component of FDAMA, Congress provided incentives to sponsors to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant an additional 6 months of marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of certain drugs in pediatric populations. The objective of section 111 was to pro-

mote pediatric safety and efficacy studies of drugs. With the valuable information generated by these studies, the product labeling can then be updated to include appropriate information on use of the drug in the pediatric population. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request issued by FDA and submit the results of those studies in an NDA or supplement.

In 2002, Congress renewed this authority when it enacted the Best Pharmaceuticals for Children Act (BPCA). BPCA also mandates that FDA report to the Pediatric Advisory Committee, in a public forum, any safety concerns during the 1 year period after we grant pediatric exclusivity. To date, we have reported safety concerns on 34 drugs at six separate public advisory meetings.

Finally, BPCA contains important, new disclosure requirements. Outside of BPCA, the Agency generally may not publicly disclose information contained in an IND, unapproved NDA, or unapproved supplemental NDA. Once FDA approves an NDA or supplemental NDA, the Agency can make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

However, section 9 of BPCA gives FDA important new disclosure authority. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request, the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric application is an approval, approvable, or not-approvable action. Thus under FDAMA, information on pediatric studies conducted in response to Written Requests was not available until after the supplemental application was approved. In contrast, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies is publicly available regardless of the action taken on the application. Since 2002, FDA has posted the summaries of these reviews for 41 products submitted in response to a Written Request on FDA's website at: (<http://www.fda.gov/cder/pediatric/Summaryreview.htm>). This information provides a rich source of valuable safety information to allow pediatricians to make more informed decisions about whether and how to use these drugs in their patients.

Post-Marketing Safety Studies

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

FDA may request that the sponsor conduct post-marketing studies to provide additional important information on how a drug works in expanded patient populations or to identify safety issues that occur at very low frequency or in special patient populations. The post-marketing safety study obligations in section 130 are of keen interest to patient and consumer advocates who track the completion of post-marketing commitments and FDA's efforts to review study results and modify drug labeling. The regulations implementing section 130 provide FDA with a mechanism to monitor study progress through the annual submission of study status reports. FDA posts the status of post-marketing studies on its public website and publishes an annual summary of industry's progress in fulfilling post-marketing commitments in the *Federal Register*.

CRITICAL PATH

On March 16, 2004, FDA released a report addressing the recent slowdown in innovative medical therapies submitted to FDA for approval: "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." The report describes options to modernize the medical product development process to try to make it more predictable and less costly. The report focuses on ways that FDA could collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path much faster, predictable, and less costly.

Enhancing the Safety of Medical Products

During drug development, safety issues should be detected as early as possible. However, because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. Despite efforts to develop better methods, some tools used for toxicology and human safety testing are outdated. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population

was not representative of eventual recipients. Conversely, some models create worrisome signals that may not be predictive of a human safety problem.

There are opportunities for developing tools that can more reliably and efficiently determine the safety of a new medical product. To meet this challenge, FDA has called for a new focus on modernizing the tools that applied biomedical researchers and product developers use to assess the safety and effectiveness of potential new products. Many of these tools—diagnostics such as pharmacogenomic tests and imaging techniques—would also be used after marketing to monitor safety in the real world clinical setting. The Critical Path report describes opportunities for FDA, working with academia, patient groups, industry, and other government agencies, to embark on a collaborative research effort. The goal is to create new performance standards and predictive tools that will provide better answers about the safety and effectiveness of investigational products, to do this faster and with more certainty, and to enhance the safety of these products in the clinic.

In addition to improved safety tools, Critical Path also focuses on tools that will help individualize therapy. We enhance safety when the target population does not include individuals who cannot benefit from the treatment. For these individuals, drug exposure is all risk. Better tools for individualized therapy will help to identify patients who will respond to therapy. New science has provided the basic knowledge to make these tools a reality.

Critical Path is not a fundamental departure for FDA, but rather builds on the Agency's proven "best practices" for expediting the availability of promising medical technologies. While the report touches on all aspects of medical product development, identifying new tools to address drug safety challenges would represent a giant step down the Critical Path.

CONCLUSION

At FDA, providing the American public with safe and effective medical products is our core mission. We base decisions to approve a drug or to keep it on the market if new safety findings surface on a careful balancing of risk and benefit to patients. This is a multifaceted and complex decision process, involving scientific and public health issues. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, as we strive for continuous improvement, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives.

Once again, thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.

The CHAIRMAN. As the next panel takes their place, I will go ahead with introductions. On the next panel we have Dr. Cecil B. Wilson, who is an internist from Winter Park, FL and a member of the AMA Board of Trustees since 2002. Dr. Wilson has been in private practice of internal medicine in Central Florida for 30 years. He is board certified in internal medicine and a member of the American College of Physicians. Dr. Wilson will discuss the impact on prescribers of changes in the way FDA communicates.

Also I have Mr. Keith L. Carson, Chairman of the Williamsburg BioProcessing Foundation. Mr. Carson started the foundation in 1994 and currently serves as the organization's chairman. He edits BioProcessing Journal, a print journal that features articles adapted from selected presentation given at the foundation's conferences. Mr. Carson will discuss the impact of new technologies on drug safety and how FDA can improve its processes, including through the developing of reference materials.

Dr. Raymond Woosley is a pharmacologist whose research has been published in over 250 publications, and has investigated the basic and clinical pharmacology of drugs for the drug treatment of arrhythmias and the cardiac toxicity of drugs. In January of 2005 he assumed the position of the President of the Critical Path Institute, C-Path, a nonprofit corporation formed by the Food and Drug Administration, SRI International and the University of Arizona to

accelerate the developing of safe innovative medicines. Dr. Woosley will discuss his ideas on how to increase the industry capabilities to develop innovative methods for accelerated drug discovery and development and how the FDA may have to change to adapt to these new methods.

We have Dr. Bruce Psaty. Dr. Bruce Psaty is a Professor of Medicine and Epidemiology and Co-Director of the Cardiovascular Health Research Unit at the University of Washington in Seattle. A practicing general internist at Harbor View Medical Center, he is a cardiovascular disease epidemiologist with interest and expertise in pharmacoepidemiology, pharmacogenetics and drug safety. He will discuss his recommendations for improving FDA's drug safety process.

I thank the panel and we will begin then with the testimony of Dr. Wilson.

STATEMENTS OF CECIL B. WILSON, M.D., MEMBER, AMERICAN MEDICAL ASSOCIATION BOARD OF TRUSTEES, WINTER PARK, FL; KEITH L. CARSON, CHAIRMAN, THE WILLIAMS-BURG BIOPROCESSING FOUNDATION, VIRGINIA BEACH, VA; RAYMOND WOOSLEY, M.D., PhD, PRESIDENT, THE CRITICAL PATH INSTITUTE, PROFESSOR OF MEDICINE AND PHARMACOLOGY, UNIVERSITY OF ARIZONA, TUCSON, AZ; AND BRUCE M. PSATY, M.D., PhD, PROFESSOR OF MEDICINE, EPIDEMIOLOGY AND HEALTH SERVICES, CO-DIRECTOR, CARDIOVASCULAR HEALTH RESEARCH UNIT, UNIVERSITY OF WASHINGTON, SEATTLE WA

Dr. WILSON. Good morning, Chairman Enzi and members of the committee. My name, as you have heard, is Cecil Wilson. I am a member of the American Medical Association's Board of Trustees and a practicing internist in Winter Park, FL.

On behalf of the AMA I would like to thank you for holding today's hearings and for inviting us to participate. Today I will discuss how FDA decisions regarding drug approval postmarketing surveillance, product labeling, off-label use and risk management impact practicing physicians like myself. I will also discuss the AMA's recommendations to improve drug safety and minimize the impact on physicians' ability to practice medicine.

Our recommendations include more active approaches to post-marketing surveillance, a final FDA rule on package inserts, the preservation of off-label prescribing, and continued collaboration between the FDA, the pharmaceutical industry and physicians to develop better risk communication tools. Approving a prescription drug or biologic for marketing is a primary way in which the FDA affects physician practice.

Since PDUFA was passed in 1992 new drugs are getting to market faster and importantly, and as you heard earlier, studies have shown that this has been accomplished without increasing the number of drug withdrawals. The AMA hopes that any new efforts to enhance drug safety can be accomplished without reversing this trend. As more drugs become available, the AMA recognizes the need to improve postmarketing surveillance. Such efforts would enhance our ability to identify rare but potentially serious adverse events in a timely fashion. So the AMA supports active approaches

to postmarketing surveillance. For example, well-designed studies on newly marketed drugs would help to quickly assess the risk of these drugs once they are in actual clinical use.

Another primary way in which FDA decisions affect physicians is through product labeling, especially the package insert. The package insert is designed and intended to inform physicians about risk and benefits of a drug. Unfortunately, today's package insert has become a long and complicated really legal document rather than a useful resource for physicians.

In my own practice when a patient presents who is on a new drug from another physician or when I simply want to check or double check the dosage of a particular drug, I, as well as other physicians, look up a drug's package insert. The problem we encounter is that the package insert contains so much information that it makes it difficult to find what we really need. So information such as dosage, contraindications, major risk and potential drug interactions are often varied within the highly technical text of the document.

In the year 2000 the FDA issued a proposed rule to make the package insert more user friendly for physicians. The AMA supports this effort and urges the FDA to finalize this rule. Further, the FDA should ensure that physicians' ability to prescribe drugs off label not be impeded. In some instances prescribing a product off label is the most appropriate therapy based on the latest and best scientific evidence, and for some patient populations it may be the only treatment.

Finally, Mr. Chair, over the past few years the FDA has opposed a number of risk management tools to enhance drug safety. Some of these tools may be useful, but some could lead to unintended consequences such as decrease patients' access to valuable medical treatments. For the vast majority of prescription drugs the patient insert, combined with effective postmarketing surveillance should constitute the risk management plan. Additional risk management tools such as patient agreements, enrollment programs or tools that create special rules for prescribing should be used only as a last resort to keep products with unique and important benefits on the market.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Wilson follows:]

PREPARED STATEMENT OF CECIL B. WILSON, M.D.

The American Medical Association (AMA) appreciates the opportunity to present its views on ways to ensure drug safety in this country and the implications for practicing physicians. We commend the Chairman and Members of this Committee for holding this important hearing. The AMA shares a common goal with Congress and the Food and Drug Administration (FDA) to optimize the benefit/risk balance of drug therapy and minimize the risks of prescription drug and biologic products.

As our Nation's drug regulatory agency, the FDA ensures that beneficial drug products are made available to the public with labels that contain adequate information about the product's risks and benefits, and protects the public from false claims. While the FDA's approval process is considered the "gold standard" around the world, the FDA's determination that a product is safe and effective is not meant to signal an absence of risk. Drug and biologic products, by their very nature, carry with them certain risks, some of which are discovered after approval. Pharmaceutical manufacturers, the FDA, physicians and patients all play essential roles in minimizing those risks and enhancing the benefits of prescription drugs and biologics.

The AMA supports the FDA's proposals to improve the format and content of the package insert, which is the portion of a drug product's labeling directed primarily to physicians. We have also been a proponent of more widespread use of the MedWatch program (FDA's adverse event reporting system) by encouraging physicians to participate. More recently, the AMA provided testimony and commentary on specific FDA initiatives related to the risk management of prescription drugs, including their concept paper on "Risk Management Programs" and their draft guidance for industry on the "Development and Use of Risk Minimization Action Plans" (Attachments 1 & 2).

This statement will focus on how FDA decisions impact practicing physicians through the drug approval process; postmarketing surveillance efforts; product labeling developed to guide physicians in the appropriate use of medications; policies on unlabeled uses; and risk management. In addition, we make recommendations to improve drug safety and minimize the impact on physicians' ability to practice medicine, including: more active approaches to post marketing surveillance; final FDA rules on the format and content of package inserts; the preservation of physicians' ability to prescribe medications for unlabeled uses; and collaboration between the FDA, pharmaceutical industry, and physicians to develop better risk communication tools.

FDA DECISIONS AFFECTING PHYSICIAN PRACTICE

Drug Approval

The FDA's decision to approve a prescription drug or biologic product for marketing moves that product from an investigational status to an approved product available for widespread use. Approving a prescription drug or biologic for marketing is the primary way in which the FDA affects physician practice. Over the years, the FDA approval process has resulted in access to a wide array of prescription drug and biologic products for use by physicians in the care of their patients.

Fifteen years ago, a primary complaint about the FDA was that the drug approval process was too slow. The problem was referred to as a "drug lag" because at the time, the United States stood well behind other industrialized countries in getting needed drugs to market. After numerous complaints, the government began to focus its attention on improving FDA drug review timelines. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), which authorized the FDA to collect user fees from companies that produce drug and biologic products. Under PDUFA, these fees were provided in exchange for an FDA agreement to meet drug-review performance goals, which emphasized timeliness. PDUFA was reauthorized by the Food and Drug Administration Modernization Act (FDAMA) of 1997 (PDUFA II) and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PDUFA III).

These acts required the FDA to: (1) speed agency review of New Drug Applications (NDAs) and Biologic Licensing Applications (BLAs); (2) improve the efficiency of drug development before submission of new drug or biologic applications; and (3) further improve the quality and efficiency of drug development, review, and risk management for newly approved products—all without compromising safety. According to the FDA, before PDUFA, the agency approved about 40 percent of the new drugs introduced on the world market either first or within 1 year of their introduction in another country. After PDUFA and through 2002, this percentage had nearly doubled. Additionally, the median total review time for new drugs and biologics decreased from approximately 23 months to 12 months, with even shorter median approval times for drugs designated for priority review.

Concern has been expressed about the number of drugs approved under PDUFA that have been withdrawn for safety reasons. However, an FDA analysis showed the rate of withdrawal for safety reasons of "new molecular entities" pre-PDUFA was 2.7 percent, while the rate post-PDUFA was 2.5 percent. This is not a significant difference. Thus, it appears as if the FDA has met its obligations under PDUFA to increase the efficiency of the drug review process without compromising the safety of approved drug products. *Therefore, the AMA and its physician members hope that any new efforts to improve drug safety can be accomplished without reversing the improvements that have occurred in the drug approval process.*

Postmarketing Surveillance

If formal postmarketing studies are not conducted by manufacturers or clinical investigators to obtain safety information, observational data collected by physicians, other health professionals, and patients are the cornerstone for evaluating and characterizing a drug's risk profile in actual clinical use. Currently, the FDA maintains an adverse event reporting system termed MedWatch, which incorporates both a

mandatory adverse event reporting system for manufacturers subject to the Agency's postmarketing safety reporting regulations, and a voluntary, adverse event reporting system for health care professionals, consumers, and patients. MedWatch can be an effective tool for detecting signals suggesting that a drug may be associated with a rare, but serious, adverse event.

However, the MedWatch program is a passive system and it is limited by its reliance on voluntary reporting, which inevitably leads to under reporting. Under reporting and uncertainty about the actual extent of drug exposure, make it difficult to estimate true rates of occurrence of drug-induced adverse events. Because of their observational nature, spontaneous reports also are limited in their ability to establish causality. Given the limitations of spontaneous reporting systems, concerns have been raised about the FDA's ability to detect serious adverse events that occur during the postmarketing phase of a drug product's life cycle. Thus, as efforts are devoted to improving drug safety, attention should be directed toward enhancing postmarketing surveillance by using more active approaches. For example, well designed pharmacoepidemiologic studies on newly marketed drugs could enhance our ability to more accurately determine a drug's adverse event profile in a timely manner.

Recently, the FDA announced its intent to create an independent Drug Safety Oversight Board comprised of FDA staff as well as medical experts from other Department of Health and Human Services agencies and other government departments to oversee the management of important drug safety issues. The AMA has not taken a position on this issue.

In addition, the FDA pledged to "expand existing communication channels and create new ones to ensure that established and emerging drug safety data are quickly available to the public (and physicians) in an easily accessible form with the intent of enabling patients and their health care professional to make better-informed decisions about individual treatment options." One of these proposed channels would be a new "Drug Watch" Web page for emerging data and risk information, and the AMA applauds these efforts to enhance transparency. *However, the FDA must provide clear advice when it disseminates emerging or preliminary information prior to taking regulatory action.*

Product Labeling

Product labeling decisions are made by the FDA in collaboration with the drug sponsor, usually the manufacturer. The product labeling includes the materials and language that comprise the product's packaging, label and package insert. The package insert is that portion of the approved labeling that is directed primarily to physicians to inform them about a product's risks and benefits, and to provide guidance on the conditions of appropriate use. However, today's package insert has become a barrier to effective risk communication, serving more as a legal document rather than a resource of useful information for practicing physicians. The FDA has recognized this problem and in December 2000, it issued a proposed rule to modify the format and content of the package insert with the goal of making the information more useful and user-friendly to physicians. Their recommendations included a more simplified, "Highlights of Prescribing Information" section within the package insert. *The AMA continues to strongly support FDA efforts to make package inserts more useful and user-friendly for physicians and encourages the FDA to issue a final rule to that effect.*

Unlabeled/Off-Label Uses

In an effort to strengthen drug safety, the FDA recently announced its commitment to sponsoring an Institute of Medicine study on drug safety systems with an emphasis on the postmarketing phase, including the study of unlabeled (also known as off-label) use. Unlabeled uses are defined as the use of a drug product for indications or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved by the FDA for marketing may be labeled, promoted, and advertised by a manufacturer for only those uses for which the drug's safety and efficacy have been established. The manufacturer submits data to the FDA demonstrating substantial evidence of efficacy and safety for each labeled indication. Even though PDUFA has reduced the review time for efficacy supplements (i.e., Supplemental New Drug Applications or SNDAs), manufacturers are not required to and may choose not to seek FDA approval for all useful indications. One major reason for not submitting an SNDA is because the expense of regulatory compliance may be greater than the eventual revenues expected (e.g., if patent protection for the drug product has expired, or if the patient population affected by the new use is very small). A sponsor also may not seek FDA approval because of difficulties in

conducting controlled clinical trials (e.g., for ethical reasons, or due to the inability to recruit patients).

A physician may choose to prescribe a drug for uses, in treatment regimens, or in patient populations that are not part of the FDA-approved labeling. The decision to prescribe a drug for an unlabeled use is made by the physician in light of all information available and in the best interest of the individual patient. Prescribing for an unlabeled use requires the physician to use the same judgment and prudence as exercised in medical practice for it to conform to accepted professional standards. Given the prevalence of unlabeled uses and the fact that in many clinical situations such use may represent the most appropriate treatment, the prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care. Therefore, the AMA has had longstanding policy:

“That a physician may lawfully use an FDA approved drug product for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion (Policy 120.988, AMA Policy Compendium).”

The position of the FDA on physician prescribing of unlabeled uses supports that of the AMA. The FDA’s published statement that addresses the appropriateness and legality of prescribing FDA-approved drugs for unlabeled uses includes the following:

“The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature (FDA Drug Bulletin. 1982; 12:4–5).”

It is important to emphasize that the AMA strongly supports the SNDA process to add new uses for drugs to FDA-approved labeling. *However, given the disparity between the actual submission of SNDAs and the evolution of evidence-based medical practice, physician prescribing for unlabeled uses should not be impeded by any actions taken to improve drug safety.*

Risk Management of Prescription Drug Products

In 1999, an FDA Task Force published “Managing the Risks from Medical Product Use.” Subsequently, in the context of PDUFA III, the FDA agreed to provide guidance for the regulated industry on risk management activities for drug and biological products. In addition to conducting a Part 15 Hearing on risk management in 2002, the FDA issued three Concept Papers (“Premarketing Risk Assessment,” “Risk Management Programs,” and “Risk Assessment of Observational Data.”) for comment in 2003, and then released three “draft” Guidances for Industry, (“Premarketing Risk Assessment,” “Development and Use of Risk Minimization Action Plans [RiskMAPs],” and “Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment”) in 2004. A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.

Routine risk minimization measures include use and revision of the package insert, combined with postmarketing surveillance. These measures should constitute the risk management plan for the vast majority of drug and biologic products. The draft guidance on RiskMAPs identified several additional tools that could be considered in designing risk minimization plans when reliance on the package insert as the primary tool may be inadequate. These tools can generally be placed under the following three categories:

- *Targeted education and outreach* (e.g., physician letters; training programs for physicians or patients; medication guides);
- *Reminder system, processes or forms* (e.g., patient agreements or acknowledgment forms; certification programs for physicians; enrollment of physicians and/or patients in special educational programs; specialized systems or records that attest to safety measures having been satisfied); and
- *Performance-linked access systems* (e.g., prescription can be ordered only by specially certified physicians; use of compulsory fulfillment systems; product dispensing only to patients with evidence of lab tests results or other documentation).

Implications for Physicians. In government’s efforts to improve drug safety, there may be a desire to use, more routinely, those risk minimization tools that extend beyond *targeted education and outreach* to include a more pervasive use of tools associated with *reminder systems and/or performance-linked access systems*. *A number of these approaches would directly manage or restrict physician prescribing and may have unintended consequences.*

These unintended consequences include:

(1) preventing some patients (who would benefit from higher risk drugs) from having access to them because of added burdens on the prescriber;

(2) prescribing of less effective, less studied, and even less safe alternative drugs that are not subject to restrictions because they are simply much easier to use;

(3) employing multiple and complex risk management tools that may be confusing to both physician and patient and, potentially result in unintended medication errors;

(4) creating administrative burdens for physicians that would likely result in the drug not being prescribed at all (unless the restricted drug is truly innovative); and

(5) possibly adversely impacting pharmaceutical company research and development in promising areas where restrictive risk management of drugs is anticipated.

Rather than focus on restrictions, the AMA believes that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it and act on it when prescribing a drug. The AMA previously proposed potential ways to improve risk communication about drugs to physicians in its comment letters to FDA on risk management (see Attachments 1 & 2).

High level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk drug products with unique and important benefits on the market. *The AMA encourages the FDA and the product sponsor to work with relevant physician organizations to assure that the minimum number and least intrusive RiskMAP tools are selected to achieve the risk minimization objective.*

Recommendations

The AMA is pleased to offer the following recommendations to the Committee. We believe these recommendations will both improve drug safety and not adversely impact how physicians practice medicine. The recommendations are as follows:

1. Improved postmarketing surveillance for potential adverse events can be achieved without slowing down the premarket drug approval process. The AMA supports the use of more active approaches to enhance postmarketing surveillance.

2. The FDA should issue a final rule, as soon as possible, implementing modifications to the format and content of the package insert with the goal of making the information more useful and user-friendly to physicians.

3. Physician prescribing for unlabeled uses should not be impeded because prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care.

4. The package insert, combined with effective postmarketing surveillance, should constitute the risk management plan for the vast majority of drug and biologic products. When this is insufficient to ensure an appropriate level of drug safety, then effective risk communication to physicians should be the primary means to reduce risks of drugs. The AMA urges the FDA and the pharmaceutical industry to collaborate with physician organizations to develop better risk communication vehicles and approaches. High level risk minimization tools, such as performance-linked access systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

The AMA once again, commends the Committee for holding today's hearing, and we thank the chairman for the opportunity to present our views. We look forward to working together on this important issue.

Attachments

1. AMA Letter 7/6/04 to FDA RE: Draft Guidance for Industry on "Development and Use of Risk Minimization Action Plans" [Docket No. 2004D-0188]

2. AMA Letter 4/29/03 to FDA RE: Risk Management [Docket No. 02N-0528]

The CHAIRMAN. Thank you very much, and I very much appreciate your concise testimony. Your entire testimony will be a part of the record, and that gives us more time for questions too.

Mr. Keith Carson.

Mr. CARSON. Mr. Chairman, members of the committee, I want to thank you for inviting me to come talk to you today.

I am a chemical engineer, different than a number of your panelists in my discipline and background, actually trained as a process engineer, and have been working for over 25 years in helping companies scale up and produce biological products at large scale, in-

cluding vaccines, antibodies, recombinant proteins, and even some of the newer products that are now coming out. So I will give you I hope a slightly different perspective.

In my organization, again, I started 10 years ago, we find ourselves in a fairly unique position I believe, and at times being a neutral party that can work with both FDA and with industry since we really have no affiliation with either, and that is a position we have been in several times in helping to develop what are called reference materials.

Biological products are very, very difficult to not only manufacture but to characterize and understand exactly what they are or to compare one product to another. This is where reference materials come in. By being able to establish a well-characterized reference material, then the manufacturers can compare their products to this one standard or this reference material.

So the most successful project to date is one where an adenovirus was produced and is now currently being stored at ATCC. It is being used throughout the world as a reference material for validating internal reference materials and their assays.

I cannot tell you enough how difficult some of these products are not only to manufacture but to regulate. They are all different. Most of the discussions here are about drugs or chemically formulated products, but when you get into biologics it becomes incredibly more complex. We have a group that are now known or being called "well-characterized biologics," including the monoclonal antibodies, recombinant antibodies, recombinant proteins. But beyond that then you have viral products, viral vaccines, bacterial vaccines. And then on top of that the cellular products, the cell therapy products are incredibly difficult to produce and to produce on a consistent basis. The lot to lot variability is very, very difficult to maintain.

One reason I am bringing this up is the people that we have there at FDA are not only receiving more and more submissions, they are having to work on more and more complex products all the time, products that they are just now trying to get their arms around and figure out the best way to try to regulate them, and even figure out what questions to ask.

The U.S. is considered to be the world leader in this technology. We certainly lost our edge in many other manufacturing and technology areas, but throughout the world we are considered the technology source for biotechnology and for biological processing. Our meetings that we hold in Europe and in Asia, they still want us to bring 70 percent of our speakers from North America. So we have a leadership role in the world here and we are highly respected, not only from a processing standpoint and technology standpoint, but from a regulatory standpoint. These other countries harmonize their regulations to a great extent around what has been done here and developed here by the FDA.

All of these products have risks, as Dr. Woodcock mentioned, even Tylenol as she mentioned. She did not use the generic name, but—or the marketed name, but all of these products have risk. The important thing is to try to define the patients that can tolerate these products the best and give them these products and then identify the patients that would have adverse events, and that is

where I think we will talk about some of these new technologies that might help us move in that direction.

Thank you.

[The prepared statement of Mr. Carson follows:]

PREPARED STATEMENT OF KEITH L. CARSON

I am a chemical engineer with over 25 years experience in the biopharmaceutical industry. My training is as a process engineer, and my focus has been on the large-scale production of biological products including viral vaccines, antibodies, recombinant proteins, viral gene vectors, and cellular therapies.

I also received an MBA in marketing from George Washington University in Washington, DC, and lived on Capitol Hill from 1981 to 1993.

I helped found the Virginia Biotechnology Association and have served as a board member for 7 years, plus one term as the association's president. I currently serve as an advisor to the board, and provide advice on biotech business development for the State and Hampton Road area.

In 1994, I founded the Williamsburg BioProcessing Foundation, or "WilBio," in Virginia Beach, Virginia. WilBio is a biotech information company that publishes the **BioProcessing Journal**TM, and organizes 12 international conferences on the development and production of biological products for human health care.

Our mission is to help develop safe and effective biological products, and our objectives are to make product development less costly, provide a trained workforce for the biotech industry, and improve communication between FDA and industry, and the academic processing centers.

Since 2000, WilBio has signed several FDA Co-Sponsorship Agreements for the development of viral reference materials. Our role has been to serve as a facilitator and coordinator for Working Groups, which manage the development of these materials and are made up of representatives from FDA, industry, and academia. In 2002, the first project resulted in the production of a well-characterized adenovirus, which is now used by product sponsors throughout the world to validate assays and internal reference materials.

Also through a Co-Sponsorship agreement, this is the 3rd year that WilBio has helped organize and manage the Annual FDA Science Forum, which is held at the DC Convention Center in May. With approximately 2,000 attendees from government, industry, and academia; this unique meeting offers the best opportunity to learn about the scientific interests and activities at FDA, and how science is used to help formulate policy and regulate products.

I have just completed a lengthy analysis of FDA's Critical Path Initiative, and have written a review article for our publication. A copy of this article has been submitted to the committee, and additional copies are available upon request. As you will note, key concepts for this initiative include: well-characterized reference materials, standardized analytical methods, shared characterization and clinical data, and improved regulatory guidelines. I have proposed that working groups be formed to tackle these issues in a fashion similar to the one taken for the highly successful adenoviral reference material project.

Today, I am here to testify about Drug Safety, and specifically the impact that new technologies could have on drug discovery, development, and approval. While these technologies appear to offer tremendous potential, their use and implementation are still in a very early stage; and a number of technical, logistical, and ethical issues must be resolved.

Technological advances in sensors, analytical methods, instrumentation, and computing power are happening so quickly that it is very difficult to know how they can best be applied, or understand what the information they generate actually means. Some breakthroughs are occurring, but many years will be required to devise the correlations needed to make the data useful.

To keep up with these technological advances and use them in the regulatory process, FDA must be properly funded to staff and equip their labs, plus train their personnel. Product reviewers must be familiar with these technologies and how to apply them, as well as comprehend the sponsor data that is submitted.

The Agency also needs a permanent Commissioner who can provide consistent leadership, policy, and direction.

EXECUTIVE SUMMARY

I am here to testify about Drug Safety, and specifically the impact that new technologies could have on drug discovery, development, and approval. While these tech-

nologies appear to offer tremendous potential, their use and implementation are still in a very early stage; and a number of technical, logistical, and ethical issues must be resolved. The technologies receiving the most attention include: microarray technology, *in silico* models, datamining, and proteomics.

Technological advances in sensors, analytical methods, instrumentation, and computing power are happening so quickly that it is very difficult to know how they can best be applied, or understand what the information they generate actually means. Some breakthroughs are occurring, but years will be required to devise the correlations needed to make most of this data useful.

To utilize the technologies, patient samples are analyzed for differences in genetic markers, or in the application of proteomics, differences in expressed proteins that can be linked with genetic markers. In particular, researchers are looking for genetic markers that could be associated with the uptake of a particular drug, or even its metabolism. In other applications, specific genetic markers could be related to potential adverse events.

Personalized medicine is based on matching drug treatments with the patient-specific genetic markers that could predict a more favorable outcome. With this approach, a higher chance of success could be predicted with certain treatments, and adverse events could hopefully be avoided.

However, there are a number of technical, logistical, and ethical issues involved with the use of these techniques. First, a patient must submit to having his genetic profile determined and analyzed, and many individuals are concerned about how this data might be used. Certain genes have already been linked to a predisposition for various diseases, and the patient could be barred from insurance or certain types of employment if this information were accessible.

In addition, very large computing power will be needed to hold the vast amount of data that will be generated. Then when numerous product sponsors want to share their data, the hardware requirements become even greater, and patient confidentiality could be further compromised. And if correlations are developed, the reasons for any relationships may not be known for many years.

To keep up with these technological advances and use them in the regulatory process, FDA must be properly funded to staff and equip their labs, plus train their personnel. Product reviewers must be familiar with these technologies and how to apply them, as well as comprehend the sponsor data that is submitted.

The CHAIRMAN. Thank you.

Dr. Woosley.

Dr. WOOSLEY. Chairman Enzi and members of the committee, as I was introduced, I am the President of a newly formed nonprofit organization created to facilitate innovations in drug development. Our goal is to create a forum for drug development that does not exist where scientists from the FDA, academia and the drug industry can bring innovations into drug development, innovations that will give patients the earliest possible access to the safest possible medications.

We believe that such a forum can spawn innovation from scientific interchange by serving as a neutral territory, free of the regulatory environment that limits most interactions of the FDA with the industry.

I am also Director of the Center for Education and Research on Therapeutics called CERT, and interdisciplinary center funded by AHRQ. Our CERT is one of 7 centers authorized by Congress in FDMA, the Food and Drug Modernization Act, to work with the FDA to improve the medical outcomes from therapeutics. Drug safety is included in that. In my testimony today I will recommend changes in drug development, drug regulation and drug surveillance that address a crisis, and I do not use that word lightly. I took it out of my testimony probably three times, but I want to emphasize that I have thought about this a great deal and I do believe there is a crisis and I hope I can convince that that word is not hyperbole.

I think this crisis in drug development translates into a crisis in the future in public health. My concern is for the long-term viability of the pharmaceutical industry and the likelihood that without change patients will have even less access to new medical therapies in the future. There are numerous signals of this crisis and they are listed in my written testimony. The following are a few that I hope will convince you that I am not over-using that word.

The pharmaceutical industry now spends an average of 12 to 15 years and almost a billion dollars for each drug that it successfully develops. Yet with all of that investment of time and money, too often it fails to detect serious adverse effects of its products until they have been on the market usually for years and millions of patients have been exposed to harm. Also these unnecessarily long billion dollar development programs leave only 2 to 5 years of market time before generic competition begins. This short amount of time to make back a billion dollars plus large profits and lack of competition from other products results in unacceptably high drug prices, prices so high that Americans are going to other countries to buy their medicines.

Over the last 10 years what has happened? The pharmaceutical industry has increased its investment in R&D by 250 percent. But what has happened from that 250 percent? The number of products, significant new products submitted to the FDA for review has fallen by 50 percent. Drug failures during testing have doubled, tens of billions of dollars in development dollars were lost when 17 drugs were removed from the market. Many patients suffered serious injury, and hundreds of class action lawsuits now threaten the very existence of some of our Nation's most successful companies.

So while the issue of drug safety must be addressed—and I am very pleased you are having these hearings—I encourage you to do so in the context of this broader crisis in which the wrong action, as you, Chairman Enzi, did mention earlier, could really have unintended consequences and could further threaten the future viability of the U.S. pharmaceutical industry, and therefore, the availability of vital new medicines.

For example, adding a requirement for Phase IV studies to our broken system without other important changes could be catastrophic. Any changes to the system must really simultaneously correct the flaws that are in our current system that leads to 12 to 15 years of development and billions of dollars expended, and it must create an efficient, effective postmarketing drug surveillance system.

Other recommendations are in my testimony, but the following are my two major points. The FDA needs more options for regulatory action. I recommend creating an optional new process of stages approval of drugs, and it is described in this article which I would like, if you would, to add to the record. The details are there, and I would be glad to answer questions about that.

The CHAIRMAN. Without objection.

[The article follows:]

[Editors Note—Due to the high cost of printing, previously published materials submitted by witnesses may be found in the files of the committee.]

Dr. WOOSLEY. This track would not result in earlier marketing, but more close surveillance of all drugs.

My second recommendation is that the FDA should be adequately funded to carry out its mission. The budget should include funds for FDA's Critical Path Initiative that was mentioned by Dr. Woodcock. That is a very important addition to this because it will improve the process to accelerate the development of safe drugs.

Because a major part of drug safety is safe use of drugs, FDA and AHRQ should be given adequate funds to create together a comprehensive multifaceted safety surveillance system. We have to create something new that does not exist, and in my written testimony I describe the characteristics of an important community-based safety network that is needed for the early detection and quantification of drug adverse events, something that is not going to be available by data dredging and data mining of the currently available databases.

In summary, drug safety problems are only a symptom of a flawed system of drug development. In the Critical Path Initiative the FDA has offered to be part of the solution to this serious problem. The Critical Path Initiative is a great investment because it has the potential to improve drug safety, facilitate drug development and to substantially reduce the future costs of medications, especially the \$720 billion estimated for a Medicare prescription drug benefit.

Thank you.

[The prepared statement of Dr. Woosley follows:]

PREPARED STATEMENT OF RAYMOND L. WOOSLEY, M.D., PH.D

Senator Enzi and members of the committee, I am Dr. Raymond Woosley, President of The Critical Path Institute, a non-profit organization created to facilitate innovations in drug development. Our goal is to create a forum for drug development scientists from the FDA, academia and the pharmaceutical industry to evaluate innovations in drug development; innovations that will give patients the earliest possible access to the safest possible medications. We believe that such a forum, i.e. a neutral territory, is essential to bring about needed changes in the ways drugs are developed. The Institute is working closely with the FDA Commissioner's office and other scientists at the FDA, The University of Arizona and SRI International (formerly Stanford Research Institute) to develop a formal arrangement for this collaboration. I am also the Director of the Center for Education and Research on Therapeutics (CERT), a Center at the University of Arizona funded by the Agency for Healthcare Research and Quality. CERT is one of seven centers in the Nation authorized by Congress to improve the medical outcomes from therapeutics. After 30 years of research and teaching in medical schools at Vanderbilt University, Georgetown University and most recently the University of Arizona, I will leave my academic position in July to lead the CERT and The Critical Path Institute. This will enable me to focus my efforts on what I believe is a crisis in pharmaceutical development.

A CRISIS IN DRUG DEVELOPMENT

This crisis can best be appreciated by looking at recent events and the following data:

1. The pharmaceutical industry spends 12–15 years and almost a billion dollars for each drug that is successfully developed. Yet, in spite of such an investment in time and dollars, this process still fails to detect serious adverse effects of products until they are on the market, often for years, and millions of Americans have been exposed to potential harm.

2. Pharmaceuticals have been one of our Nation's most successful industries. However, over the last 10 years, the industry increased its investment in research and development by 250 percent but the number of new products submitted for FDA review has fallen by 50 percent.

3. The proportion of drugs that fail during development has doubled in the last 10 years.

4. In the last 8 years, over half of the 15 drugs removed from the market because of safety concerns were, in fact, safe when used as directed in the labeling. Warning labels did not prevent drugs from being used in ways that resulted in harm to patients. Tens of billions of research and development dollars were wasted and many patients suffered serious injury.

5. Personalized medicines, the promise of human genome research, are only rarely being developed because of the high cost of drug development relative to the potential market size.

6. The protracted and costly development of drugs, combined with the limited time in the market before generic competition begins, results in unacceptably high drug costs and drug re-importation from countries that employ price controls.

7. Skyrocketing estimates for the cost of a Medicare prescription drug benefit have prompted consideration of policies and pricing negotiations that would limit access to new medicines and threaten future research and development of medicines that are needed by patients with chronic and debilitating diseases.

8. In addition to concern for the patients harmed by drugs, there is another societal concern. The removal of drugs from the market has resulted in hundreds of class action law suits that threaten the very existence of some of our Nation's most successful companies.

So, while the issue of drug safety must be addressed, we must do so in the context of a broader crisis in which the wrong action(s) could further threaten the future viability of the pharmaceutical industry and the availability of vital new medicines. For example, adding a requirement for phase IV monitoring to our broken system without other changes would be catastrophic. At the same time, the absence of an effective drug safety program is one of the major contributors to the delays in drug development that adds to high costs and delayed access to important new medicines. Two-thirds of the FDA medical reviewers recently surveyed expressed concern that the post-marketing surveillance system at the FDA was inadequate. I have no doubt that this concern must have a negative influence the reviewers' willingness to assist the industry in accelerated development of even the most important new medicines. Therefore, it is essential and timely that we discuss how to improve the development of drugs and assure their safe use.

BASIC "FACTS OF LIFE" FOR PHARMACEUTICALS

A critical first principle is that there is no such thing as a "safe drug". Even the title of these hearings, "Ensuring drug safety" is an impossible goal. No one can ensure drug safety; we can only expect the FDA to identify drugs with an acceptable risk/benefit ratio, inform the public, and develop methods to maximize benefit and minimize harm. FDA approval will never mean that a drug is "safe." Instead it signifies that the available evidence indicates that a drug should be "relatively safe when used as directed." All medicines that have pharmacologic effects must be assumed to have the potential for harm. This is a message that must be better appreciated by the public so that they are not surprised when newly marketed drugs are found to have adverse effects.

THE FDA MUST BE GIVEN ADEQUATE NUMBERS OF PEOPLE AND RESOURCES

Over the last 20 years I have served as a frequent advisor to the FDA, usually on issues of drug safety. In this capacity, I learned first hand the limitations that exist in the FDA's legal authority as well as the FDA's limited resources. It doesn't appear in their budgets but information technology and computer allocations have been slashed in recent years. The agency that handles some of the most complex and vital data in the world relies upon information handling systems that were discarded decades ago in most corporations. Only 109 scientists monitor the safety data from over 3,000 prescription drugs. Where a complete system of drug safety surveillance is needed, the FDA is forced to rely on its voluntary reporting system for adverse events.

THE FDA LACKS ADEQUATE LEGAL AUTHORITY TO EFFECTIVELY REGULATE DRUGS

Once a drug is marketed, the FDA has no control over the way it is used in clinical practice. Relatively safe drugs are often used in unsafe ways (e.g. in combination with other interacting drugs or in excessive dosage or duration). As is the case in Canada and other countries, the FDA should be given the authority to restrict or suspend access to drugs when serious questions arise about their safety.

The FDA also lacks any authority to demand further research on marketed drugs. Warning labels, though commonly required by the FDA, are known to be ineffective. The only effective tools that the FDA has to protect the public are, (1) to keep a drug off the market or, (2) once on the market, try to take it off. Because of its lim-

ited resources, the FDA rarely attempts legal action to remove drugs from the market. In almost every case, drugs are voluntarily removed by the manufacturer because of pressure from the FDA and not deliberate legal action by the FDA.

A BETTER TOOL BOX

The FDA needs more options for action. The FDA could better perform its responsibility if it had a broader range of options with which it can respond to the ever broadening spectrum of drug information that is generated over the pharmaceutical life of a drug.

A PROPOSAL FOR STAGED APPROVAL OF NEW DRUGS

Because more information than ever before is being generated about the value and risks of new drugs and because time is required for this information to be assimilated into the practice of medicine, there is a need for earlier approval followed by tightly controlled and more gradually increasing usage of new medications. Figure 1 demonstrates an alternative path for new drugs that I believe should be considered, debated and evaluated. It proposes an earlier approval but more gradual growth in use of a prescription drug combined with a comprehensive safety assessment in the marketplace. As can be seen, there is an earlier and more gradual rise in the number of patients treated in this model. This allows time for more complete safety testing and assimilation of the drug into the practice of medicine before millions are exposed to the drugs.

The first change suggested is in phase II, which would be expanded to include more complete characterization of the drug's dose-response relationship in the intended population and sub-populations (e.g. the very elderly, those with renal insufficiency, co-morbid conditions, etc) and for completion of any necessary targeted drug interaction studies. These latter studies should be those based on *in vitro* predictions, e.g. cytochrome P450 or drug transporter interaction studies. Phase II should include modern computing techniques such as *in silico* simulation of trials, enrichment using biomarkers, adaptive trial design and others suggested in the FDA's Critical Path Initiative.

Market-I: At the end of a more comprehensive and informative phase II requiring approximately 4 years, the drug could be approved for marketing to a carefully defined population of patients (Market-I in figure 1). This is very similar to the way AIDS drugs were developed in 2-4 years without taking dangerous shortcuts.

A Safety System: To make the early release of a drug feasible and rationale, it will be essential to have an intensive plan for post-marketing safety assessment and risk management. Academic programs such as the Centers for Education and Research on Therapeutics (competitively funded by the Agency for Healthcare Research and Quality to improve outcomes from medical therapies) can help develop risk management programs and conduct outcomes research on large databases and registries to confirm the efficacy and safety predicted from phase II. As they evaluate the safety of the drug, they can also use similar methods to confirm efficacy for initial indications and evaluate the potential efficacy of the drug in new indications. In most cases, the new drug should initially be given under observed conditions, using a system like the yellow card system in the U.K. in which physicians report the outcome of therapy in each patient receiving a specific drug on a "yellow card." Modern electronic medical record systems make it possible to have a system like the U.K.'s General Practitioner's Network which tracks the outcome of every patient they treat with a new drug. Also, modern electronic registries can detect adverse event signals earlier and compare the safety of new and older drugs in a class. The CERTs could play a role similar to the pharmacovigilance centers in France and monitor drug outcomes in the community. The FDA and the pharmaceutical sponsor would have to agree to the use of measures to assure that the drug is used as directed in labeling. Sponsors could be encouraged to follow the lead of at least one innovative company that paid commissions to sales representatives based upon how well doctors in their region used the company's drug instead of how often the drug was prescribed. Effective risk management programs have been successfully developed in the past for drugs with the potential for serious toxicity, e.g. clozapine. Because this antipsychotic drug can cause fatal bone marrow toxicity in 1 percent patients per year of treatment, proof of monitoring of white blood count is required before the drug can be dispensed. This has reduced the incidence of fatal toxicity by 60 percent.

A Novel System: In Arizona, The Critical Path Institute and the CERT are exploring the feasibility of developing an innovative community based safety surveillance system. This system would resemble programs in the UK and France in that it would prospectively gather data on the outcomes of new medicines and submit it

directly to the FDA. I believe that such a system must be developed de novo because the information needed to address drug safety cannot be gleaned from currently available databases. Data mining only works when the information you need is somewhere in the system. For the same reason, linking databases will never give adequate information. The system must be relatively inexpensive, should not interfere with the practice of medicine or pharmacy and should be flexible enough to detect suspected and unsuspected adverse events of any newly marketed drug. It should be able to quantify the rate of adverse event occurrences and even answer questions of relative safety by comparing the outcomes with selected comparator drugs. It should provide positive feedback to physicians in order to prevent future adverse events and improve drug outcomes. If the system were effective, even drugs with the potential for serious adverse events might be able to remain on the market. For this or any program to be successful, the FDA must be given the staff and resources to participate in the design and implementation of this system and then to monitor the data that are gathered from this system.

The staged approval model would allow a pharmaceutical company to begin marketing its product earlier with a lower total capital investment and at a time when much more of the patent life is still in effect. It should also make it possible to detect any serious life-threatening problems earlier before millions have been exposed, reducing the frequency of litigation and class action law suits. Also, for companies using this track, serious consideration should be given to offering indemnification from law suits filed for adverse events in return for the sponsor paying for any medical expenses resulting from such adverse reactions. This would provide patients and the drug sponsor some protection from the potential harm from a new drug.

Market II: If after a period of careful observation on the market, the drug appears safe and effective, it could be given approval for an expanded market with fewer or no restrictions to its use (Market II on the diagram). Market II is effectively the same as the current market in which any licensed physician can prescribe a marketed drug for any indication, as long as the physician has evidence that such use has a scientific basis.

Pharmacist Assisted Care (PAC) and OTC: If a marketed prescription drug is found to be relatively safe and used for a condition that can be self-diagnosed by the patient, it has been customary for it to be given non-prescription status, often called "over-the-counter" or OTC. This may or may not be attractive to the pharmaceutical sponsor depending upon many economic and market factors. In some cases the sponsor would like to expand the market by having the drug available OTC. However in many cases such as the statin drugs for lowering cholesterol, some aspect of a drug's use requires medical supervision and the FDA is reluctant to approve its use without medical supervision. In these cases, there is no alternative now available but to deny approval of OTC status. However, in Canada and many other countries there is another option. The drug can be given "behind the counter" status. "Behind the counter" means that the drug is available in pharmacies for patients who ask for the medication but only after consultation with a pharmacist. The pharmacist can perform any pre-screening or counseling that could make it more likely that the drug will be used safely. This additional step, "Pharmacist Assisted Care" (PAC), could widen the therapeutic benefit to patients, better utilize the important role of pharmacists and minimize the risk of therapy. After a period of safe use in the PAC category, a drug may be recommended for full OTC status when justified.

THE NEED FOR INNOVATIONS IN THE PROCESS OF DRUG DEVELOPMENT

To address the increasing delays and failures in drug development, the leadership of the FDA has proposed the "Critical Path Initiative". This proposal includes efforts to optimize drug development and identify new ways to test medicines that will give greater assurance of safety and effectiveness than we have now. However, this plan will require new partners and new resources for the FDA. A recent report from former Secretary of Health and Human Services (HHS), Tommy Thompson, pointed out the need for partnering between FDA and the NIH, CMS and CDC. But to do this collaborative work, it must have resources that are not provided in the current budget. Also, the fact that the FDA budget is under the Department of Agriculture and not under the full control of the Secretary of HHS is an impediment to forming these partnerships.

The FDA's Critical Path Initiative calls for academic partnerships to develop innovations that improve drug development. Forming these will also require that the Agency have the staff and resources to participate. Just as the Moffet Center in Illinois was established by the FDA to address food safety, academic sites can be "neutral ground" where scientists can share their knowledge and expertise in drug devel-

opment and drug safety without commercial conflicts of interest. These public/private partnerships can enable scientists from the FDA, academia and industry to develop methods to increase the efficiency and informativeness of the drug development process.

The Critical Path Institute that I lead was created for this purpose. Out of serious concern over the relative safety and availability of new medicines, the citizens of Tucson and Southern Arizona have committed over \$9 million to seed the initial work of the Institute.

We believe that an investment that enables the FDA to facilitate the development of safe drugs is a good investment, especially at this time. Medicare estimates that its prescription drug benefit will cost over \$720 billion in its first 10 years. That estimate surely assumes that new drug costs will continue to rise at its current rapid rate. If we are ever going to have less expensive new drugs, we must shorten the development time, increase the number of drugs successfully developed in order to stimulate competition in the marketplace and improve the safety information about these drugs. Increased numbers of drugs for a specific disease enable competition to yield lower drug prices. Larger numbers of drugs with different actions will better meet the needs of our biologically diverse population. "One size" does not "fit all." Furthermore, adequately studied drugs and the safe use of drugs can result in lower healthcare costs and improved health.

Lowering drugs costs by accelerating the development of safer medications is a far better alternative than "re-importation" of drugs which is just an indirect means to use foreign price controls to lower our consumers' drug costs. It would be preferable to give the FDA the resources it needs to help improve the process of developing drugs.

SUMMARY OF RECOMMENDATIONS

1. Permanent experienced leadership for the FDA is essential. Acting Commissioner Lester Crawford, Acting Deputy Commissioner Janet Woodcock and many others working with them are experienced leaders who can, with the proper resources, lead positive change at the FDA.

2. The FDA should be adequately funded to carry out its mission. This support should include funds for the Critical Path Initiative and an effective safety surveillance system.

3. The "user fee" system should be replaced with a system in which industry support is not directly linked to the FDA's work and performance.

4. Determination of drug safety requires an assessment of both risk and benefit and should remain the purview and responsibility of the FDA, and not of a separate agency as I and others have previously suggested. However, the on-going safety evaluations of marketed drugs should be made by FDA scientists who were not responsible for the original approval recommendation.

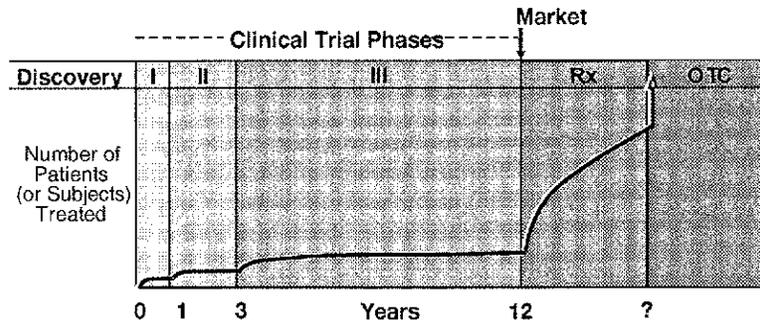
5. The FDA should develop a comprehensive post-marketing assessment program for drugs using inter-agency collaborative programs and public-private partnerships.

6. Just as the National Transportation Safety Board is responsible for investigating all accidents and then makes recommendations for safety, there should be an analogous independent body to conduct in-depth review of the process used to detect serious issues/events in drug development and the response to those events by the FDA and industry. This body could assess the roles played by consumers, healthcare providers, health professions educators, the FDA, the pharmaceutical industry, the press and even Congress.

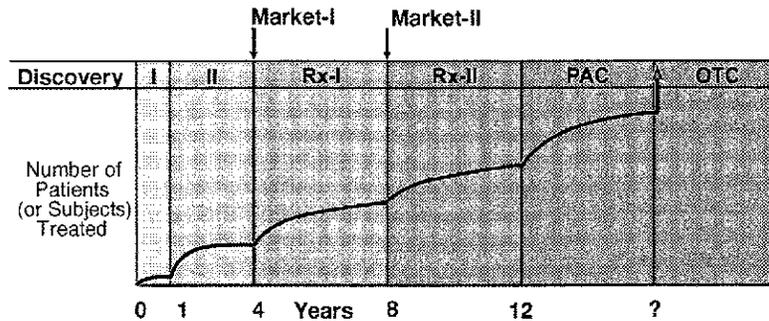
7. The FDA should be given the authority to release drugs in stages that are appropriate for the drugs' level of development and the information that is known at the time.

I am extremely grateful for the opportunity to provide testimony at this hearing. I hope you find my perspective of value as you review the FDA's drug safety system.

Drug Development 2005



Staged Approval Track



The CHAIRMAN. Thank you very much.

Dr. PSATY. Thank you very much. Thank you for the opportunity to testify. My name is Bruce Psaty and, as you indicated, I am a general internist and a cardiovascular disease epidemiologist. I have broad interests in public health and drug safety.

The COX-2 inhibitors, a new class of nonsteroidal anti-inflammatory drugs, were supposed to have fewer serious side effects than other available nonsteroidals. After more than 5 years on the market, an increased risk of heart attack, stroke were confirmed for Vioxx, Celebrex and Bextra. Some of the 20 million Vioxx users and 27 million Celebrex users were injured. Indeed, the integrity of the American Drug Safety System has been called into question. How can this problem be prevented in the future?

Recommendations:

No. 1. Give balanced attention to risks and benefits in the FDA decisions. To use a drug wisely, patients and physicians need to know about both risks and benefits. The design of the preapproval trials of the COX-2 inhibitors minimized the possibility of uncovering evidence of cardiovascular harm. Some of the trials with unfa-

orable results went unpublished. If manufacturers do not address the potential risks, as well as benefits, with equal scientific rigor, then, in the interests of public health, the FDA must insist that they do so, both before and after approval.

No 2. Require large long-term trials. The limited preapproval of the evaluation of the COX-2 inhibitors was not adequate. Medicines that will be used by millions of Americans for long periods of time are best evaluated in large, long-term clinical trials that are started as early as possible in the approval process. These trials need not delay the approval. This approach used for the lipid-lowering statin drugs has benefited patients, physicians and the pharmaceutical industry.

No. 3. Create an independent Center for Drug Safety within the FDA to oversee drugs after marketing. In a commentary, entitled, "Postmarketing surveillance—lack of vigilance, lack of trust," the editors of JAMA write, "It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek to prove itself wrong." Other scientists and former FDA officials have also advocated an independent Center for Drug Safety.

No. 4. Invest the Center for Drug Safety with new authority to regulate drugs that are on the market. Revisions to the Vioxx product label took 2 years. The Center for Drug Safety must be able to compel manufacturers in a timely fashion to revise labels, to conduct patient education or physician education, to limit advertising, to complete promised studies, to conduct new studies, to suspend sales or to withdraw drugs. The Center for Drug Safety should be responsible for postmarketing evaluations, including the determinations of the risks and benefits for drugs that are on the market.

No. 5. Provide the Center for Drug Safety with new resources. America has become the drug safety testing ground for new medications, such as COX-2 inhibitors. According to Dr. David Kessler, former head of the FDA, "PDUFA should have had funding on the safety side from the beginning, but industry refused to accept that. We wanted it. The industry said, no."

Senator Enzi, you referred to the drug lag. And your committee did terrific work in solving the drug lag. We now have a safety lag, and I would encourage you to address the safety lag. In the Office of New Drugs, more than 1,000 employees work to review a few dozen new drugs each year. In the Office of Drug Safety, 109 employees work to evaluate the safety of thousands of drugs that are currently on the market. The FDA needs an independent center whose mission, vision and values are geared toward evaluating and monitoring drugs that are on the market.

No. 6. Strengthen postmarketing safety systems. The FDA's MedWatch system, which has been characterized as a fundamentally 1950s approach, lacks many of the features of high-quality epidemiologic studies, including the ability to validate events by standard criteria, the ability to identify controls and so forth. The State of this system stands in stark contrast to the enormous expansion of the pharmaceutical industry during the past several decades. In 2004, the COX-2 inhibitors had combined sales of more

than \$6 billion. Several new mechanisms to conduct postmarketing surveillance rapidly and efficiently merit support.

In summary, regardless of the speed of approval, toxic molecules occasionally make it to market as drugs. To protect the health of the public, the most important recommendation is an independent Center for Drug Safety with new authority and funding. Ongoing congressional oversight of the FDA, of CDER, and the new Center for Drug Safety would afford an important opportunity for the public discussion of drug safety.

Thank you.

[The prepared statement of Dr. Psaty follows:]

PREPARED STATEMENT OF BRUCE M. PSATY, M.D., PH.D.

Mr Chairman and members of the committee, thank you for the opportunity to testify. My name is Bruce Psaty. As a practicing general internist and cardiovascular-disease epidemiologist, I have broad interests in public health and drug safety.

The COX-2 inhibitors, a new class of non-steroidal anti-inflammatory drugs, were supposed to have fewer serious side effects than other available non-steroidals. After more than 5 years on the market, an increased risk of heart attack and stroke has been confirmed for Vioxx, Celebrex, and Bextra (1–5). Some of the 20 million Vioxx users and 27 million Celebrex users have been injured. Indeed, the integrity of the American drug-safety system itself has been questioned. How can this problem be prevented in the future?

RECOMMENDATIONS

1. Give balanced attention to risks and benefits in FDA decisions (6–8). To use a drug wisely, patients and physicians need to know about both risks and benefits. The design of the pre-approval trials of the COX-2 inhibitors minimized the possibility of uncovering evidence of cardiovascular harm. If manufacturers do not address the potential risks and benefits with equal scientific rigor, then in the interests of public health, the FDA must insist that they do so, both before and after approval.

2. Require large long-term trials (9). The limited pre-approval evaluation of the COX-2 inhibitors was not adequate. Medicines that will be used by millions of Americans for long periods of time are best evaluated in large long-term clinical trials that are started as early as possible in the drug approval process. These trials need not delay approval. This approach, used for the lipid-lowering statin drugs, has benefited patients, physicians and the pharmaceutical industry.

3. Create an independent Center for Drug Safety within the FDA to oversee drugs after marketing (10–14). In a commentary entitled, “Postmarketing surveillance—lack of vigilance, lack of trust,” the editors of *JAMA*, write: “It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong.” Other scientists and former FDA officials have also advocated a truly independent Center for Drug Safety.

4. Invest the Center for Drug Safety with new authority to regulate drugs that are on the market (4,15). Revisions to the Vioxx product label in 2002 took more than 2 years to negotiate. The CDS must be able to compel manufacturers, in a timely fashion, to revise product labels, to conduct patient or physician education, to limit advertising, to complete promised studies, to conduct new studies, to suspend sales and to withdraw drugs. The Center for Drug Safety should be responsible for post-marketing evaluations, including determinations of the balance of risks and benefits for drugs that are on the market.

5. Provide the Center for Drug Safety with new resources (14,16,17). America has become the drug-safety testing ground for new medications, such as the COX-2 inhibitors. According to Dr. David Kessler, former head of the FDA, “PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that . . . We wanted it. The industry said no.” Since 1992, FDA resources for drug safety have dwindled. In the Office of New Drugs, more than 1,000 employees work to review a few dozen new drugs per year. In the Office of Drug Safety, 109 employees work to evaluate the safety of thousands of drugs currently on the market.

6. Strengthen US post-marketing safety systems (18-21). The FDA's MedWatch system, which has been characterized as "fundamentally a 1950s-era approach," lacks many of the features of high-quality epidemiologic studies, including validation of events by standard criteria, complete ascertainment of cases, population-based controls, comparable assessment of drug use and risk factors, and so forth. The state of this system stands in stark contrast to the enormous expansion of the pharmaceutical industry during the past several decades. In 2004, the three COX-2 inhibitors alone had combined sales more than \$6 billion dollars. Several new mechanisms to conduct post-marketing surveillance rapidly and efficiently merit support.

Regardless of the speed of approval, toxic molecules occasionally make it to market as drugs. To protect the health of the public, the most important recommendation is an independent Center for Drug Safety with new authority and funding. Ongoing congressional oversight of the FDA, CDER, and the new Center for Drug Safety would afford an important forum for the public discussion of drug safety. Thank you.

SUPPLEMENTARY INFORMATION

Post-marketing surveillance. When drugs are approved as "safe and effective" for their intended use, the known benefits appear to outweigh the known risks (20). At the time of regulatory approval for most drugs, a number of issues remain unknown—the occurrence of rare but serious adverse drug events, drug interactions, late events during treatment or after the discontinuation of treatment, effects in pregnancy or differential effects in subgroups that may be defined by age, sex, race, or other factors. In contrast to the highly structured pre-marketing evaluation, post-marketing surveillance has little structure. According to Gale, "the regulatory process creates an evidence-free zone at the time of launch of new drugs" (20). Pharmaceutical companies often promise post-marketing clinical trials as a condition of approval. In practice, however, more than half of these promised studies, according to an FDA report, have not been started (15). The FDA lacks authority to insist that these promised studies be completed or to compel new post-marketing studies. The FDA post-marketing regulations require only that pharmaceutical companies collect, review and report to the FDA all suspected adverse drug reactions (ADRs) thought to be associated with the drug (22,23). While both companies and the FDA can analyze the ADR data and recommend actions such as label changes, additional warnings, or new studies, the FDA regulations largely focus on reporting procedures and thus leave unclear who is required to initiate these actions.

U.S. post-marketing surveillance system. MedWatch, the FDA safety information system and adverse event reporting program, encourages physicians to report ADRs on a voluntary basis (18). Although the FDA received 286,755 ADR reports in 2001 (24), these data have major well-known limitations. The MedWatch ADR data are suitable only to identify rare serious adverse drug events that occur early in treatment and that are unrelated to the indication of the drug. For example, the lipid-lowering statin drug, Baycol (cerivastatin), was withdrawn from the market in 2001 because it was associated with high rates of rhabdomyolysis, a breakdown of muscle cells that causes pain, kidney failure and sometimes death (19,21,25). The MedWatch ADR data lack many of the features of high-quality epidemiologic studies, including validation of events by standard criteria, complete ascertainment of cases, population-based controls, comparable assessment of drug use and risk factors, and so forth. It would not have been possible to use the MedWatch system to detect reliably, for instance, the increased risk of cardiovascular events associated with the COX-2 inhibitors. One recent commentator characterized the MedWatch system as "fundamentally a 1950s-era approach" (26).

Growth of drug sales. The lack of development in post-marketing surveillance systems stands in stark contrast to the enormous expansion of the pharmaceutical industry during the past several decades. Although the costs of drug development are high, spending on prescription drugs between 1997 and 2001 increased by about 18 percent per year; and in 2001, the total prescription drug expenditures in the U.S. reached \$154.5 billion dollars (27). In 2004, despite the withdrawal of Vioxx in September, the three COX-2 inhibitors alone—Vioxx, Celebrex, and Bextra—had combined sales more than \$6 billion dollars, or an average of about \$16 million per day (28). The recent growth of the pharmaceutical industry has outstripped the safety systems that were developed when the industry was young.

Epidemiologic studies and new opportunities. In the past, data sources used to conduct high-quality observational studies of the risks and benefits of drugs have included existing cohort studies (29), administrative data from health maintenance organizations (30,31), Medicaid data (32,33), Medicare data linked to cancer reg-

istries (34), and international databases with drug data (35,36). In addition to AHRQ-funded Centers for Education and Research in Therapeutics (26), the FDA has had cooperative agreements with several institutions to investigate drug safety, but the available funds have diminished in recent years. Several new opportunities are on the horizon. First, data from new Medicare drug benefit can be linked with hospital and ambulatory care data to create a new resource for the study of drugs in older adults. With appropriate protections for privacy, these data should be available to the FDA and independent scientists interested in drug safety. Secondly, as part of the NIH Roadmap Project, the HMO-Research Network—Coordinated Clinical Studies Network will create an infrastructure for conducting studies on substantial numbers of the U.S. population, and the movement toward an EPICcare based electronic record among the network members should soon provide the opportunity to conduct post-marketing surveillance rapidly and efficiently.

Post-marketing clinical trials. The pharmaceutical industry supports a number of post-marketing clinical trials, often for new indications. The cardiovascular harm associated with the COX-2 inhibitors became apparent in studies that were conducted for new indications such as the prevention of non-cancerous tumors in the colon (1–3). For the lipid-lowering statin drugs, for instance, the large long-term clinical trials have provided robust evidence about their health benefits in preventing cardiovascular complications of high levels of cholesterol (37–40). On the basis of this evidence, the indications for the statin drugs have expanded, statin drug sales have increased, and the health of the public has improved. Rapid publication and widespread dissemination of favorable findings is standard practice.

Failure to publish trials with unfavorable results. Unfavorable results tend not to get published. In the manufacturer’s trial of 1.6 mg of Baycol, about 12 percent of patients developed signs and symptoms compatible with rhabdomyolysis (25). The high rate of adverse effects, with a dose that was only twice as high as the approved dose of 0.8 mg, “led to a consensus by the [company’s communications] committee not to publish the results of this study” (25). Similarly, in 2000, Pfizer completed a randomized trial of celecoxib in Alzheimer’s patients, but never published the unfavorable cardiovascular results and only made them publicly available in January 2005 (41). The results of this Alzheimer’s study were not submitted to the FDA until June 2001, several months after a safety review that established labeling for Celebrex. Human subjects participate in studies to contribute to science and public health. Failure to publish findings not only violates their trust, but it also misrepresents the evidence about risks and benefits for patients and physicians. Federal action to assure that all clinical trials are registered and reported in a timely fashion is important.

Prescription Drug Users Fee Act (PDUFA) of 1992. In the late 1980s and early 1990s, the pressure from companies and patients alike was not for additional safety evaluations, but for shorter approval times (42). In response to the criticism that the FDA approval times were too long, Congress introduced user fees in 1992. Pharmaceutical companies seeking drug approvals paid fees that enabled the FDA to hire additional staff, and the FDA was expected to meet new requirements for the timelines of new-drug approvals (16). According to Dr. David Kessler, head of the FDA from 1990 to 1997, “PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that We wanted it. The industry said no” (17). The 1992 user fee act and its reauthorization in 1997 prohibited the agency from spending users fees “on post-marketing surveillance or other drug-safety programs” (14). The reauthorization in 2003 included some provisions for safety. During the period 1992 to 2003, this approach—more and faster new approvals without additional funds for safety surveillance—relied increasingly on the honesty, trustworthiness, and integrity of the pharmaceutical industry in the conduct of its own post-marketing safety evaluations.

PDUFA, review times, and funding for safety. The PDUFA act in 1992 and its reauthorizations in 1997 and 2003 reduced the time required for review of a new drug application by the FDA from 33 months in 1992 down to about 13 or 14 months in 2001 (17). As a result, the proportion of new molecular entities that are first introduced in the U.S. has increased from 2 to 3 percent in the early 1980s up to 60 percent in 1998 (43). New medicines are now indeed available to Americans more quickly. At the same time, U.S. patients also became the first to receive new medications, some of which, such as COX-2 inhibitors, are subsequently discovered to have serious adverse effects. The Office of Inspector General 2003 Report on the FDA’s Review Process for New Drug Applications has assessed the impact of the new review process at the FDA (16). Funding for safety has also been affected. In 1992, 53 percent of the budget of the FDA Center for Drug Evaluation went to new drug reviews, and the rest went to surveillance, laboratories and other safety efforts. In 2003, 79 percent went to new drug reviews. Resources available for safety

have dwindled (44). Drug recalls following approval increased from 1.56 percent in 1993–1996 up to 5.35 percent for 1997–2001 (10).

Calls for an independent Center or Office of Drug Safety. In a recent commentary, the *JAMA* editors advocate an independent center or office of drug safety: “It is unreasonable to expect the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong (ie, that the decision to approve the product was subsequently shown to be incorrect)” (10). Other recent commentaries in *JAMA* (13) and the *New England Journal of Medicine* have recommended the creation of an independent drug-safety board “to monitor drug safety, investigate reports of drug toxicity, and recommend actions to minimize the risks of drug therapy” (14). The new Advisory Board on Drug Safety announced by Michael O. Leavitt, secretary of Health and Human Services on February 15 is not adequate. According to Dr. William Schultz, FDA deputy commissioner for policy from 1994 to 1998, “The FDA should separate the monitoring of drugs after they have been approved from the drug review function” (12).

Need for additional authority in the Center for Drug Safety. In March 2000, Merck was aware that compared with naproxen, Vioxx increased the risk of heart attacks (45). In February 2001, an FDA Advisory Committee reviewed the safety data, but revisions to the “Precautions” section of the VIOXX product label were delayed until April 2002. The public health rationale for the 2 year delay in revising the product label remains unclear. Although the FDA can call Advisory Committee meetings or issue press releases, talk papers, guidances, and requests to manufacturers, these powers are not adequate to regulate drugs that are on the market. For an approved drug, the FDA currently engages in protracted negotiations with manufacturers rather than mandating manufacturers: to change a product label, to conduct patient or physician education, to limit advertising to patients or physicians, to modify approved indications, to restrict use to selected patients, to complete post-marketing studies agreed upon at the time of approval, to conduct additional post-marketing studies or trials, to suspend marketing or withdraw a drug. At least one pharmaceutical executive has advocated providing the FDA with additional authority to mandate studies after drugs are approved (46). Moreover, provisional approval for the first 2 or 3 years would provide an opportunity to re-review the balance of risk and benefit.

Elements required to protect the health of the public. The failure to pose a question often precludes the possibility of obtaining an answer. Pharmaceutical companies generally lack enthusiasm for aggressively pursuing questions about the safety of their drugs. In science, only those questions that are investigated with well-designed studies have a decent chance of producing a solid answer. If the pharmaceutical industry does not pose critical questions about drug safety, the FDA must do so in an effort to protect the health of the public. Key elements related to the study of drug safety include: (1) the generation of ideas about a drug’s risks as well as its benefits; (2) a sustained effort to investigate or document risks as well as benefits; (3) the availability of high-quality surveillance systems or the conduct of specifically designed studies to assess risks as well as benefits; and (4) the willingness to publish findings about risks as well as benefits. If manufacturers do not provide support for a vigorous and balanced scientific evaluation of safety signals for drugs that are already on the market, the Center for Drug Safety must do so to protect the health of the public.

Activities of the Center for Drug Safety. At the time of approval for each new drug and on the basis of information available in the NDA and other studies, the Center for Drug Safety needs to identify a set of studies required to address the key unanswered questions, particularly the pursuit of potential safety “signals” or “plausible biologic hypotheses” on behalf of the health of the public. Depending on the drug, the indication and the known safety profile, the studies may include Phase IV trials, epidemiologic studies, pharmacokinetic-pharmacodynamic studies, close surveillance of ADR reports, or a combination of several approaches. Specific post-marketing trials or studies should be designed, conducted and completed in a timely fashion. The Center for Drug Safety should be responsible for assessing the balance of risk and benefit of drugs that are on the market.

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The CHAIRMAN. Thank you very much. I appreciate the testimony of all of the witnesses. I have a huge number of questions. I know I am not going to be able to get through all of them. But as I mentioned before, we will be submitting some in writing, particularly the more detailed ones.

I will begin with Dr. Wilson. One of our witnesses on Tuesday said that patients are going to doctors and getting drugs they should not because of direct-to-consumer advertising. How would you respond to that? Could you comment on the role of direct-to-

consumer advertising in educating patients and in the doctors' prescribing decisions?

Dr. WILSON. Yes, thank you, Mr. Chairman. The AMA supports patients' increased access to drug information and, clearly, direct-to-consumer advertising provides that. But let me just say, as a practicing physician, I would echo the remarks that you heard earlier this morning that it, also, exerts an enormous pressure on the physician. And so our concern is the impact direct-to-consumer advertising has on the physician-patient relationship. It, obviously, is advertising that is designed to sell a product, and we would suggest that it does not present in the ads the kind of accurate and objective information that patients need.

In 1993, the AMA published some guidelines or agreed to some guidelines in consultation with the FDA which deal with direct-to-consumer advertising. So we would urge the pharmaceutical industry to use those guidelines.

The CHAIRMAN. Thank you.

Mr. Carson, you mentioned data mining in your testimony. What are the potentials and limitations for data mining to identify safety signals early? What are the hurdles to developing a comprehensive database for use with validated mining tools? Does the FDA have the computational resources it would need to truly be able to use those databases?

Mr. CARSON. Probably not, as far as the last part of your question. The amount of data that is involved is phenomenal and is rapidly growing. One of the biggest problems is in having the data available or making it available, getting the companies to make the data available unless they are required to. There are some aspects where it is voluntary, some where it is required, some where it is just not asked for at all or it is not involved.

I think that industry needs to see the advantage of making the data available and sharing it amongst themselves. And then there is a lot of data available at the FDA that other companies do not see, but a lot of it is proprietary. They have to keep it confidential for the companies that have supplied the data. So there would have to be agreement that this data could be made available.

In addition to that, of course, is the confidentiality issues surrounding the patient. There, of course, is a lot of concern, and you see reports of this of people will be, many people will be very reluctant to have these genetic screenings done and to have that information in a database where they do not know if it is controllable or not. Of course, there was the story the other day in the paper about one of the major banks losing a lot of information on their customers. Well, I think that in general the public does not trust these large databanks or people that control this data.

So I think getting the data is probably the biggest problem. There would be ways to provide the computing capability of the cooperation were there. That is probably the easiest part, but does FDA have the resources right now? I would probably think they do not. They probably need additional funding for that.

The CHAIRMAN. Thank you.

Dr. Woosley, you indicate in your written testimony that you no longer support the idea of a separate drug safety agency and that you now believe that the determination of drug safety requires an

assessment of both risk and benefit and should remain in FDA. What made you change your mind?

Dr. WOOSLEY. Further information, and the kind of points that were made by Dr. Woodcock this morning were compelling. I think she, clearly, described the need for an ongoing evaluation of the benefits and the safety. And that really does need some memory, some corporate memory, of what the drug has done.

But the other points she made is, also, very important, and that is what the other drugs in that category might have done because often the safety assessment of one drug really needs to include the safety of all the other drugs around it and in that class. Because predicting drug safety is often knowing what the others did.

In fact, I went back and read our New England Journal article a few years ago that we wrote, and it really, what we were calling for was an oversight, like the NTSB, not that actually does the drug safety analysis, but looks at drug use, in general, and are the systems that we have in place appropriate? Are drugs being developed, regulated, and are they being used in the appropriate way, and are there places outside the FDA that need to get involved?

For example, I have taught medical students for 30 years, and I should be taking some blame when doctors misprescribe. Only 15 percent of the medical schools in this country have required courses in clinical pharmacology and therapeutics. We, as medical educators, really need to be part of solving this problem, also. AHRQ needs to be there, to be looking at the drug use. They have the drug safety programs, the medical errors programs, but it is not just the FDA that is involved. They cannot control drug use.

So, again, to answer your question more specifically, I do not support a separate, independent safety agency outside of the FDA. I think the FDA needs to be involved in the changes that they are making to bring the decisionmaking away from the people who approved it into an environment where there will be greater input, but still have the efficacy there is going to make me very happy with the changes.

The CHAIRMAN. Thank you. And I think probably local pharmacists appreciate your comments because it emphasizes the role that they play in the whole process, too.

My time is expired.

Senator Isakson.

Senator ISAKSON. Thank you, Mr. Chairman.

Following up on that question, Dr. Psaty, I take it you disagree with that.

Dr. PSATY. No. Actually, I have not advocated necessarily that the independent office be outside the FDA. I think, in many instances, the FDA has done terrific work. I would question some of the decisions they have made. But the Office of New Drugs currently dominates CDER, the drug review section, and the current structure at the FDA is just what the industry desires—a powerful engine to approve drugs and a weak effort to investigate safety in the postmarketing setting.

What the American public needs and deserves, in addition to the rapid approval of drugs, is a center whose mission is devoted to postmarketing safety evaluations.

Senator ISAKSON. So your reference to independence was independence of the original testing not independence of the Agency.

Dr. PSATY. Yes, it was. And I said in my testimony an independent center within the FDA.

Senator ISAKSON. I just wanted to make sure I understood that. Thank you.

Dr. PSATY. Yes, sir.

Senator ISAKSON. Dr. Wilson, is the insert that you have difficulty reading the same one I am supposed to read in my medicine bottle?

Dr. WILSON. Senator, I would assume that it is very similar. [Laughter.] As a matter of fact, in that regard, I frequently will move from the part I am supposed to read to the part the patient is supposed to read, and I find them equally unclear.

Senator ISAKSON. The only thing harder to read than the insert in a medicine bottle is the doctor's signature on a prescription. [Laughter.]

Dr. WILSON. And the better the doctor, the worse their writing is.

Senator ISAKSON. And I would acknowledge that I am sure legal liability plays a large role in what has to go in that information, and I understand that, having been a businessman for 33 years. And I do not like for the Government to get in the business of starting to say how big letters ought to be, and how short words ought to be and things like that, but I would say that, from a standpoint of a patient's, that information regards to warnings to a patient, which certainly is what we ought to think about, giving what we are talking about today, and that information a doctor needs with regard to what they need to know vis-a-vis warnings the patient might get, if it was a little larger or at least at the beginning of that insert, it would sure be a help to me, and I take it, it would be a help to you. I do not know if that is AMA's recommendation, but that was just an independent advertisement.

Dr. WOOSLEY, you read, and I am not sure I heard you say it, but you read in your recommendations I read that the user fee system should be replaced with a system in which industry support is not directly linked to the FDA's work and performance. Would you elaborate on that for a second.

Dr. WOOSLEY. I applaud the willingness of the pharmaceutical industry to help the Agency do its job in reviewing drugs. But when you tie it, like piecework, to the review of the drug, it really misses the real need that the Agency has for something more than just reviewing that product. When a new drug goes on the market, there are drug interactions with other drugs that can affect the safety and the use of other drugs. That is not paid for when you just pay for the review. So, by having more drugs on the market, you create more work for everybody and more surveillance.

So what I would suggest is that we come up with a way to fund the Agency, ideally, without user fees. In a perfect world, that would be the goal, but that may not be the reality. So a compromise would be to find a way that the industry can support the FDA's role in assisting them in the regulation of their products. Now, that does not mean just reviewing the NDA. It means all of the work for the FDA that the FDA needs to do to improve the

drug development process, to improve the drug surveillance system. How that is done, I mean, that is what you gentlemen and ladies are expert at, but I think the basic principle of tying it like piece-work to the product creates the wrong environment.

It, also, because of the large amount of money coming into the FDA for that part of it, and the lack of additional money for the rest of the mission, I made the analogy to, if you open up a restaurant and you sold all sorts of sandwiches, but everybody bought the roast beef, then you become a roast beef store. And that is what the FDA has become because there is so much money now going for the review process and not for the rest of its work, people think that it is beholding to the industry. It is not beholding to the industry. It is just that that part of it is well-funded. The rest of its mission needs to be funded, also.

Senator ISAKSON. My time is almost up, but I want to make sure I understand. You talked about the staged approval process. Did that mean that there would be a stage at which certain patients might get a drug before total approval took place? Is that what that meant?

Dr. WOOSLEY. That is what it means. It means that the drugs would be used in people who have been tested, that it would move into the community in a staged fashion, and as you learn more about it, then it would be expanded into the broader population.

Senator ISAKSON. Just to comment, Mr. Chairman. I think her name, Mrs. Washington Ines, I think was her name, that testified yesterday or the day before on behalf of cancer patients. That is a particular census of patients where it appears to me that would be a process well worth looking at. Is that the kind of thing you are talking about?

Dr. WOOSLEY. Exactly.

Senator ISAKSON. Thank you, Doctor. Thank you, Mr. Chairman. The CHAIRMAN. Thank you.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

I thank all of you for your willingness to be here and for the expertise that you bring.

Dr. Wilson, I have got to ask you about one thing. One, you need to know I do not hold much confidence, and have not held much confidence, in MedWatch. I think that the marketplace has changed. I think it is an antiquated program. It worked at one time, and the fact is that we cannot count too much on it regardless of how it is structured, so I am not going to ask you how to restructure it or your confidence in it.

I am concerned that in your written testimony you talked about the FDA needing to spoon-feed physicians, and I think that in the system that we have got, and certainly with the ability for physicians to make off-label decisions about prescriptions that they write, it is really incumbent on physicians not necessarily to wait for pharmaceutical reps or for the FDA or for some outside entity to share with them either the original information of a new drug or the ongoing revisions that might be learned in a postsurveillance process or in the practice of medicine.

So I am going to ask you to elaborate, if you will, exactly what you meant because I do not think I read it in the same context.

Dr. WILSON. Thank you, Senator. And I hope I did not say “spoon feed” in the testimony.

Physicians have a significant responsibility to recognize untoward effects and to take those known untoward effects of drugs into account when they are counseling with patients, be sure the patients understand both the risks and the benefits. Having gone through a college and medical school, I believe strongly that communication and education can change behavior. So I think my observation about present methods of communication, whether it is MedWatch or whether it is the drug insert, which we have discussed, I would suggest that if it is not working, it is not because communication and education cannot work, it is because it is because it is not good communication and education.

So I think we, as physicians, would suggest that we need to look at ways to communicate, and people who know how to do that do it very well. But I would not discard that because the challenge in discarding it is to put regulations which prescribe who can prescribe the medicine and under what circumstance, which put requirements on patients in terms of reporting and testing. Efforts which may well decrease adverse side effects, I would suggest, very well will decrease access to medication. So we are wedded to better communication, better surveillance, better education.

Senator BURR. I agree with you wholeheartedly, and I think communication is at the root of it. And just since 1997, when FDMA was passed, technology has changed in such a way that you no longer have a pharmaceutical reference book that you go to. First, you go to your computer. It is a much faster, easier, more complete analysis that one can receive.

There is only one problem. It has to be initiated either by an individual or by a medical professional. They have to be willing to go there and to look for the answer, but I think that the answers are available. They are certainly not available in the things that we do not know, and I encourage everybody within the system to begin to look at how we not mandate it, but continue to make it easier for individuals to want to do that.

Dr. Woosley, welcome. It is great to see you again. I have got to ask you, because I have got great pride in CERT, how is it going? Can you give us an update?

Dr. WOOSLEY. It is going great, and I really thank you, as former Congressman Burr, for being one of the champions and the visionaries that helped us create this CERT. There are seven of them now. They are competing for creating four more.

I must say, though, the biggest limitation—remember, you remember this I am sure—CERTS were created to work with the FDA. The biggest failing of the CERTs is the lack of ability to work with the FDA to the level that we need to. They do not have the budgets to send people. They send one person to each of our meetings every quarter. But day-to-day interactions with the FDA needs to occur for us to be successful in our CERTs.

That is what I was saying earlier is that because safe drugs means safe use of drugs, we need the people, like AHRQ and CERT, to be part of the solution in drug safety.

Senator BURR. I think we have heard, in a pretty coordinated fashion, both several days ago and then from this panel, that the

focus should not be on how we create something new. What we have is a system that can work if you properly fund it. If the emphasis is on making sure that you fill in the holes and the gaps that exist, and I hope that, in fact, we are going to do that, my hope, looking at the changes that have just happened again since 1997, the creation of CERT, the frustrations that I think more people share than just me with MedWatch, are that we can design something that is better. It can be within FDA. It can take the talents of professionals that we have there. It can use the expertise in the outside world of physicians and researchers across the country.

In addition to that, we now have the human genome mapping complete, and our ability now to take this to another level, whether that is within the FDA or within NIH or within HHS or within academia in this country, to be able to look at the current compounds that we have from a human genome standpoint and begin to target where we might not have picked up something that we might want to go back and look at or that raises a red flag is available, but we have got to have the initiative to go there.

So it may be that this conversation is not just about where do we go on this particular incident, but where do we go down the road based on more technology and based upon where our knowledge allows us to go. And it is refreshing to think that we could be at a point where we are not tasked with dealing with a crisis, where we are actually a visionary committee, and I think it is because of the chairman's willingness to do these hearings that we are actually focused now and, hopefully, will focus out a little bit further than just tomorrow.

Mr. Chairman, thank you.

The CHAIRMAN. Thank you.

I wish we had more time for going into this. I have about another 20 questions that I came with, and I have got another dozen questions that I have developed as a result of the things that you said, that we will need more clarification on, but we will get to those and would appreciate a response.

We have had some excellent testimony. I really appreciate your interest, the information, your attendance. The hearings that we have had on the FDA have made a great contribution I think to the debate on drug safety. The witnesses have given us the benefit of their vast and varied experience, and we have had a tremendously varied panel in all instances. They have brought us some serious and some innovative proposals to improve the system and given us a lot to think about.

I look forward to working with my colleagues on both sides of the aisle to develop a comprehensive response to the issues that have been raised in these hearings. As I mentioned, there will be further questions. Your full testimony will be in the record. You will have an opportunity to expand on any of your remarks or any of the questions that others were given as well, and those will become a part of the record. The record will be open for 10 days for that. So I thank you for your participation, and this hearing is now adjourned.

[Additional Information follows:]

ADDITIONAL INFORMATION

PREPARED STATEMENT OF SENATOR HILLARY RODHAM CLINTON

I would like to thank Senator Enzi and Senator Kennedy for convening today's hearing, and I look forward to learning more about the ways in which the FDA and private industry are using technology to further the agency's mission of ensuring the safety of medications for all Americans.

I am extremely interested in the opportunity to learn more about the FDA's Critical Path Initiative, through which the agency will identify and prioritize the most pressing drug development problems facing our public health system.

This initiative will expedite the development of new technologies that can improve the assessment of new products, allow for the use of more targeted therapies, and improve post-marketing safety monitoring.

The innovations that could result from such an initiative would be invaluable to our health system. Not only could they be used to improve the health status of Americans, but they would improve the quality of care provided to consumers, and could reduce the impact of medical errors upon the healthcare system.

While First Lady, I began my work with the FDA on developing the Pediatric Rule, which ensures that drugs marketed to pediatric populations have first been tested on children. And I've continued to work on these issues with my colleagues, including Senators DeWine and Dodd, during my time in the Senate. I know that my colleagues and I are interested in the ways that the technologies we discuss today could be used to further deliver clinically appropriate treatments to pediatric populations.

For example, genetic markers may someday allow physicians to determine how a specific patient will react to a given medication, thus removing many of the dosing uncertainties that exist in modern medicine.

I am pleased to learn that the FDA has already identified the data collected through the *Best Pharmaceuticals for Children Act* and the Pediatric Rule as the foundation for development of medications that are increasingly safe and efficacious for use in pediatric populations.

And I believe the lessons we learn from analyzing this pediatric data will benefit all patient populations with specific dosing and treatment needs—in short, all Americans.

Again, I would like to thank Senators Enzi and Kennedy for convening today's hearing, and I look forward to working with my colleagues on the HELP committee to developing some practical, bipartisan solutions to encourage the development of innovative and safe medications for American consumers.

QUESTIONS OF SENATOR CLINTON FOR JANET WOODCOCK, M.D.

Question 1. In the FDA's "Innovation or Stagnation" report, the agency mentions the research possibilities associated with the body of data collected by the FDA as a result of the *Best Pharmaceuticals for Children Act* and the Pediatric Rule. Could you please elaborate on the ways that the Critical Path Initiative might utilize this data to perform a comprehensive analysis of pediatric pharmacology, safety and efficacy?

Question 2. I was interested to learn that the technology development initiatives supported by the FDA might allow clinicians to target medications to very specific patient populations. Could you please comment on the ways in which the targeting of medications might enhance the delivery of clinical appropriate treatments to children beyond the scope of what we are currently able to achieve with the Pediatric Rule and *Best Pharmaceuticals for Children Act*?

AMERICAN MEDICAL ASSOCIATION
CHICAGO, IL 60610
July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Draft Guidance for Industry on “Development and Use of Risk Minimization Action Plans” [Docket No. 2004D-0188]

The American Medical Association (AMA) is pleased to offer its comments on the Food and Drug Administration’s (FDA) May 2004 Draft Guidance for Industry on “Development and Use of Risk Minimization Action Plans” [Fed Reg. 2004;69:25130-25132]. The AMA’s comments focus principally on Sections II-V of the Draft Guidance, and generally are consistent with AMA’s previous comments of April 29, 2003 on the FDA’s Concept Paper, “Risk Management Programs” [Docket No. 02N-0528], and of May 22, 2002 in testimony at FDA’s Public Meeting on the Risk Management of Prescription Drugs.

GENERAL COMMENTS ABOUT THE DRAFT GUIDANCE, DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS

The AMA shares a common goal with the FDA to optimize the benefit/risk balance of drug therapy and to minimize the risks of drug and biological products. However, the AMA remains concerned about the number of Risk Minimization Action Plan (RiskMAP) *tools* described in the Draft Guidance that would directly manage or restrict physician prescribing. If these tools are expanded to more pharmaceutical products, the potential for unintended consequences such as reduced patient access to necessary drugs or reduced manufacturer investments in innovative therapies is significant. Thus, the AMA continues to recommend that higher level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

On the other hand, the AMA commends the FDA for incorporating changes into the Draft Guidance that respond to some of our criticisms of the Agency’s 2003 Concept Paper on this subject. In particular, the AMA is pleased that the FDA is encouraging drug sponsors to:

- Develop RiskMAPs only for products that pose an unusual type or level of risk;
- Use RiskMAPs judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients;
- Seek the input of other stakeholders, including physicians, when planning risk minimization activities and when selecting specific RiskMAP tools;
- Apply objective criteria when determining whether a RiskMAP is necessary for a particular product;
- Select the minimum number of RiskMAP tools necessary to minimize the risk, select tools based on available evidence of effectiveness, and objectively evaluate the effectiveness of RiskMAPs and their tools using evidence-based performance measures;
- Adopt tools that facilitate the central role of the health care practitioner in controlling the risks of medical product use; and
- Consider unintended consequences of a RiskMAP, such as reduced access, as part of the sponsor’s Evaluation Plan.

The AMA offers the following comments on individual Sections II-V of the Draft Guidance.

SECTION II: BACKGROUND

The AMA agrees with the FDA that “when planning risk assessment and risk minimization activities, sponsors should consider stakeholder input (e.g., from con-

sumers, pharmacists, physicians, third-party payers).” However, the AMA believes the FDA needs to put greater emphasis on this important point in a Final Guidance.

The AMA continues to urge open communication and collaboration among the FDA, the pharmaceutical industry, and national physician organizations on the subject of risk management. Such communication and collaboration is needed at the macro level so that the FDA’s overall risk management initiative achieves an appropriate balance between the need to protect patients from harm and the need to avoid heavy-handed regulations that interfere with medical practice. Furthermore, collaboration among the FDA, a product sponsor, and relevant physician organizations also is recommended for individual product RiskMAPs, as described in the Draft Guidance, to ensure that the RiskMAP is effective, feasible and acceptable in usual health care practices.

Furthermore, the FDA also may wish to consider establishing a permanent advisory council of practicing physicians, representing a large number of national medical specialty societies, that could advise the Agency on issues like RiskMAPs on an ongoing basis.

SECTION III: THE ROLE OF RISK MINIMIZATION AND RISKMAPS IN RISK MANAGEMENT

Determining an Appropriate Risk Minimization Approach. The AMA strongly agrees with the FDA that the FDA-approved professional labeling (Package Insert [PI]), updated from time-to-time to incorporate information from routine post-marketing surveillance, is sufficient to be the routine risk minimization plan for the vast majority of drug and biological products. The information provided in the PI, along with other information about a product (e.g., published clinical trials), should remain the standard method of providing benefit and risk information to physicians about the use of a drug or biological product.

However, as previously communicated to FDA, the AMA believes that the current PI for prescription drugs is a barrier to effective risk communication because it has become a legal document rather than a resource of useful information for busy practicing physicians. In December 2000, the FDA issued a Proposed Rule to modify the format and content of the PI with the goal of making the information more useful and user-friendly to physicians. The AMA has supported this effort, especially the proposed “Highlights of Prescribing Information.” The AMA urges the FDA to issue a Final Rule implementing these changes to the PI as soon as possible.

Furthermore, the FDA should promptly develop and make readily available (e.g., via the Internet) a computerized database of the most up-to-date prescription drug labeling for all products. Such a database could have prominently placed safety alerts for new risk information on selected drugs. Physicians need to be trained to use this database for their professional labeling needs in lieu of the hard-copy *Physicians Desk Reference* (PDR) that is both cumbersome and dated for certain products.

Definition of Risk Minimization Action Plan (RiskMAP). The AMA accepts the FDA’s definition of a RiskMAP as “a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits.” Moreover, the AMA agrees with the FDA that *tools* used to meet RiskMAP goals and objectives do not apply to routine risk minimization plans, i.e., FDA-approved professional labeling.

Determining When a RiskMAP Should be Considered. The AMA agrees with the FDA that the decision to develop a RiskMAP needs to be determined on a case-by-case basis. Moreover, the AMA supports the FDA’s recommendation to use objective criteria, such as type of risk, magnitude of risk, frequency of risk, populations at greatest risk and/or those likely to derive the most benefit, existence of alternative treatments, reversibility of adverse events observed, preventability of the adverse event, and probability of benefit, when considering whether a RiskMAP is necessary. As previously discussed, the AMA encourages the FDA and the product sponsor to seek the input of relevant physician organizations in determining whether a RiskMAP is needed. This will give further assurance to physicians that the process is equitable and driven by good science.

SECTION IV: TOOLS FOR ACHIEVING RISKMAP GOALS AND OBJECTIVES

Relationship of RiskMAP Tools to Objectives and Goals. The AMA has no specific comments on this section.

Categories of RiskMAP Tools. The AMA accepts the FDA’s three categories of RiskMAP tools, i.e., targeted education and outreach, reminder systems, and performance-linked access systems.

Description of RiskMAP Tools. The AMA supports the establishment of a RiskMAP Web site by FDA. At a minimum, this Web site should contain a description of RiskMAP tools that have been used and all available evidence on the effec-

tiveness of each tool in achieving a risk minimization objective and/or goal. The AMA believes this is necessary to convince health care practitioners that a potentially burdensome RiskMAP tool can effectively improve the benefit/risk balance for a drug product.

Selecting and Developing the Best Tools. This is an especially important section of the Draft Guidance, and the AMA commends the FDA for its recommendations to product sponsors, that when selecting RiskMAP tools, to:

- Maintain the widest possible access to the product with the least burden to the health care system that is compatible with adequate risk minimization;
- Identify the key stakeholders (e.g., physicians) who have the capacity to minimize the product's risks and to define their roles;
- Seek input from these stakeholders, including physicians, on the feasibility of implementing and accepting a particular RiskMAP tool in usual health care practices;
- Use RiskMAP tools with the least burdensome effect on physician-patient relationships;
- Select tools based on available evidence of effectiveness in achieving the specified objective; and
- Consider, and seek to avoid, unintended consequences of tool implementation that obstruct risk minimization and product benefit.

The AMA also appreciates the FDA's recognition that physicians are the most important managers of product risks once a drug is marketed and, furthermore, that the FDA does not have the authority to control prescribing decisions made by physicians for their patients. The AMA strongly agrees with the FDA's view that product sponsors should recognize this central role played by physicians in controlling the risks of medical product use and should adopt tools that facilitate this role.

Only time and experience will answer the question as to whether drug product sponsors are implementing RiskMAPs that are consistent with the recommendations put forth by the FDA in this section of the Draft Guidance. The AMA is hopeful that this will be the case. When RiskMAPs are considered necessary, the AMA encourages the FDA and the product sponsor to work with relevant physician organizations to assure that the minimum number and least intrusive RiskMAP tools are selected to achieve the risk minimization objective. Whenever possible, targeted education and outreach should be the RiskMAP tools selected, and the AMA refers the FDA to our letter of April 29, 2003 to Docket No. 02N-0528 for detailed comments on how risk communication to physicians can be improved.

As stated earlier in this letter, the AMA continues to believe that higher level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market. As discussed in detail in our earlier letter of April 29, 2003, a number of potential unintended consequences, including reduced access to necessary therapies, substitution of less effective therapies that are not subject to RiskMAPs, multiple burdensome and confusing RiskMAPs that can lead to errors, and adverse effects on pharmaceutical innovation, may result if RiskMAPs with high level risk minimization tools are more commonly employed.

Mechanisms Available to the FDA to Minimize Risks. The AMA has no specific comments on this section.

SECTION V: RISKMAP EVALUATION: ASSESSING THE EFFECTIVENESS OF TOOLS AND THE PLAN

Rationale for RiskMAP Evaluation. The AMA is in strong agreement with the FDA regarding the need for well-designed studies to periodically evaluate the effectiveness of a RiskMAP. The AMA concurs that the most important evaluation is of the overall performance of a RiskMAP in achieving its targeted health outcomes and goals. However, the AMA also agrees that separate assessments should be done for individual tool performance and for acceptability of RiskMAP tools by physicians.

Considerations in Designing a RiskMAP Evaluation Plan. The AMA is in general agreement with the FDA on the details of this section. In particular, the AMA supports the following FDA recommendations:

- When possible, drug product sponsors should select well-defined, evidence-based, and objective performance measures tailored to the particular RiskMAP to determine whether the RiskMAP's goals or objectives are being achieved.
- Whenever feasible, drug product sponsors should design evaluation plans to include at least two different, quantitative, representative, and minimally biased evaluation methods for each critical RiskMAP goal to compensate for the limitations of the other.

- Drug product sponsors should periodically evaluate each RiskMAP tool to ensure it is materially contributing to the achievement of RiskMAP objectives and goals to eliminate ineffective tools and concentrate resources on useful tools.

- Drug product sponsors should evaluate RiskMAP tools prior to implementation; this should include pilot testing to assess comprehension, acceptance, feasibility, and other factors to determine how readily RiskMAP tools will fit into everyday physician practices.

- Formal evaluation plans are unnecessary for routine risk minimization plans, i.e., FDA-approved professional labeling.

FDA Assessment of RiskMAP Evaluation Results. The AMA generally supports this section on how the product sponsor reports a RiskMAP evaluation to the FDA, and that FDA will perform its own assessment of RiskMAP effectiveness.

Making Information from RiskMAP Evaluation Available to the Public. As stated earlier in this letter, the AMA supports the establishment of a RiskMAP Web site by FDA that would include descriptions of RiskMAP tools and all available evidence on the effectiveness of these tools. The AMA also believes that this Web site should contain results of evaluations of RiskMAPs that have been previously implemented to inform physicians and the public about the effectiveness of the program in meeting its risk minimization objectives and goals. While the AMA understands that some product sponsor information will remain proprietary, we believe it is in the sponsor's and FDA's best interests to be as transparent as possible about the effectiveness of a RiskMAP. Such transparency will provide credible evidence to physicians and the public that a particular RiskMAP either did or did not effectively improve the benefit/risk balance for a drug product.

ADDITIONAL COMMENTS

In our letter of April 29, 2003, the AMA offered two additional comments that have not been adequately addressed by the FDA in the Draft Guidance. First, concern has been expressed by physicians and pharmacists that it is difficult to remember the various risk management programs (now called RiskMAPs), and especially the multiple risk management (RiskMAP) tools, currently employed for various drug products. This is because each risk management program has been uniquely developed for a specific drug product and, therefore, all of the current programs are different in their requirements. However, in Section IV(D) of the Draft Guidance, FDA continues to suggest that the best RiskMAP tool or tools be selected on a *case-by-case* basis.

To address this concern, the AMA encourages the FDA, in collaboration with the pharmaceutical industry and other stakeholders (e.g., physician organizations), to take a more systems-based approach to RiskMAPs. Appropriate tools should be prospectively developed based on evidence of effectiveness, and a standard set of tools for each level of risk should be part of a standard "toolbox" of RiskMAP tools. When a product meets the criteria for a RiskMAP at a certain level, to the extent possible, a standard set of tools should be employed in that product's RiskMAP. At a minimum, any given tool should be consistent across products.

The AMA's other comment that was not addressed in the FDA's Draft Guidance regards the incorporation of RiskMAPs for drug products into more global quality assurance programs. The AMA believes that the FDA, the pharmaceutical industry, physician organizations, and other stakeholders need to consider the incorporation of risk management (RiskMAPs) for drug and biological products into more global quality assurance programs. As electronic health records (EHRs) and E-prescribing become more common and they are electronically linked to other aspects of care (e.g. lab test results), it should be possible to effectively incorporate RiskMAPs, as part of overall quality assurance, into the normal routine of physician practice. As an analogy, the Physician Consortium for Performance Measurement, convened by the AMA, is currently developing physician performance measures derived from evidence-based practice guidelines. The AMA is working with physician group practices that have EHRs to incorporate the performance measures into their systems so that satisfying the performance criteria becomes a routine part of medical practice.

CONCLUSION

In conclusion, the AMA appreciates the opportunity to comment on the FDA's Draft Guidance for Industry on "Development and Use of Risk Minimization Action Plans." We hope that our insight into the issues discussed in the Draft Guidance proves helpful for the FDA as it moves to finalize this Guidance. We look forward to working with the Agency as it continues its activities in this area.

Sincerely,

MICHAEL D. MAVES, M.D., MBA

AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILLINOIS 60610
April 29, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
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RE: Risk Management [Docket No. 02N-0528]

The American Medical Association (AMA) is pleased to offer its comments on the Food and Drug Administration's (FDA) Notice on risk management activities for drug and biological products that was issued in the March 7, 2003 Federal Register. The AMA's comments focus principally on Sections II-V of the FDA Concept Paper, "Risk Management Programs," and generally are consistent with the AMA's testimony at the FDA's Public Meeting on the Risk Management of Prescription Drugs on May 22, 2002. We further address the FDA's question about improving the quality of spontaneously reported case reports [of adverse events], which was part of the FDA Concept Paper, "Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment."

GENERAL COMMENTS ABOUT THE CONCEPT PAPER, RISK MANAGEMENT PROGRAMS

The AMA has had a longstanding commitment both to improving the quality of medical care delivered by physicians to patients and to promoting efforts to improve patient safety. In furtherance of this goal, the AMA established the National Patient Safety Foundation in 1997 and has participated in a number of initiatives on clinical quality improvement. The AMA also has been a partner and strong supporter of MedWatch, the FDA's adverse event reporting program. As such, the AMA shares a common goal with the FDA to optimize the benefit/risk balance of drug therapy and to minimize the risks of drug and biological products.

However, a number of the risk management tools described in the FDA's Concept Paper would directly manage or restrict physician prescribing. The AMA has serious concerns about the potential unintended consequences if these tools were expanded to more pharmaceutical products. We are particularly concerned that the use of these risk management tools could prevent some patients who would benefit from higher-risk drugs from having access to them, or that potential restrictions on prescribing could serve as a deterrent to manufacturer investments in innovative therapies. As expressed in our testimony last year, the AMA is also concerned that the FDA, and drug sponsors, may be attempting to regulate the practice of medicine through some of these risk management tools in ways that exceed the FDA's statutory authority.

Other than the AMA's testimony at the FDA Public Meeting in May 2002, we are unaware of any input from national medical specialty societies on the FDA's risk management initiatives. The AMA believes it is essential that there be open communication and collaboration among the FDA, the pharmaceutical industry, and national physician organizations on this subject. Such communication and collaboration is needed at the macro level so that the FDA's overall risk management initiative achieves an appropriate balance between the need to protect patients from harm and the need to avoid heavy-handed regulations that interfere with medical practice. Furthermore, collaboration among the FDA, a product sponsor, and relevant physician organizations also is recommended when a risk management program, as described in the Concept Paper, is being contemplated for a specific drug or biological product.

SECTION II: IMPORTANT RISK MANAGEMENT CONCEPTS

The AMA strongly agrees with the FDA that the Package Insert (PI), as defined in this section of the Concept Paper, combined with routine postmarketing surveillance should constitute the risk management plan for the vast majority of drug and biological products. The information provided in the PI, along with other information about a product (e.g., published clinical trials), should remain the standard method of providing benefit and risk information to physicians about the use of a drug or biological product.

However, the AMA believes that the current PI for prescription drugs is a barrier to effective risk communication because it has become a legal document rather than a resource of useful information for busy practicing physicians. In December 2000, the FDA issued a proposed rule to modify the format and content of the PI with the goal of making the information more useful and user-friendly to physicians. The

AMA has supported this effort, especially the proposed “Highlights of Prescribing Information.” The AMA urges the FDA to issue a final rule implementing these changes to the PI as soon as possible.

Furthermore, the FDA should promptly develop and make readily available (e.g., via the Internet) a computerized database of the most up-to-date prescription drug labeling for all products. Such a database could have prominently placed safety alerts for new risk information on selected drugs. Physicians need to be trained to use this database for their professional labeling needs in lieu of the hard-copy *Physicians Desk Reference* (PDR) that is both cumbersome and dated for certain products.

SECTION III: WHEN WOULD AN RMP BEYOND THE PACKAGE INSERT BE APPROPRIATE?

The AMA accepts the FDA’s definition of a risk management program (RMP) as “a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert” (see Section II of the Concept Paper). Thus, the remainder of the AMA’s comments will assume a drug or biological product requires a Level 2, 3, or 4 RMP, as defined in Section IV of the Concept Paper.

The AMA agrees with the FDA that the decision to develop an RMP for a particular product, and the level of the RMP, needs to be determined on a case-by-case basis. This will depend on the severity of the risks when compared to the magnitude of the benefits for a drug or biological product, and the likelihood that an RMP would lower the risks without adversely affecting the benefits. As discussed above, the input of relevant physician organizations in this decision-making should help the FDA and the product’s sponsor select the most appropriate RMP for the product.

To help determine whether any drug or biological product needs an RMP, as well as the level of the RMP, the AMA believes it would be useful for the FDA, the pharmaceutical industry, and physician organizations to collaborate on the development of objective criteria for making this determination. Severity of risk, frequency of risk, reversibility of risk by an effective RMP, importance of product benefit to patient outcome, and availability and relative benefit/risk of alternative therapies are among the factors that should be considered in developing criteria for determining whether an RMP is needed. This collaborative development of objective criteria to determine the need for an RMP would give some assurance to all stakeholders that the process is equitable and driven by good science.

SECTION IV: WHAT INTERVENTIONS OR TOOLS ARE AVAILABLE FOR USE IN ACHIEVING RMP GOALS AND OBJECTIVES?

The AMA has a number of comments on this section of the Concept Paper. In making our comments, we have assumed the Level 1–4 categorization scheme, as proposed by the FDA under Section IV(D), is applicable.

Physician education (Level 2) should be the risk management tool used for most drug and biological products that need an RMP.

The AMA believes that the FDA should promote physician education through improved risk communication as the tool that should be used for most drug and biological products that need an RMP. Level 3 and Level 4 RMPs should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

Based on our experience at the May 2002 Public Hearing, the AMA is concerned that the FDA has a predetermined view that risk communication to physicians is ineffective in modifying prescribing behavior to minimize risk. For example, the FDA considers the effectiveness of traditional “Dear Doctor” letters that are mailed to physicians when new and important risks are discovered to be questionable. While this may be true, it is an indication that more innovative and effective approaches to physician education about risk need to be developed, not an indication that Level 3 and 4 RMPs should be more frequently employed. The AMA urges the FDA to work with all stakeholders to make physician education through improved risk communication an effective—and the preferred—RMP for most products.

The AMA believes that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it, accept it, and act on it when prescribing a drug. At the May 2002 Public Meeting, the AMA presented a number of potential ways to accomplish this goal. Most of these options could be implemented immediately, including:

- The FDA, the pharmaceutical industry, and physician organizations should undertake a major CME initiative on risk communication. Physicians need to be aware of labeling changes that identify serious adverse events and that, in some cases, these serious adverse events can be minimized by modifications in prescribing. The

AMA's recommendations that the FDA publish its final rule on the PI and create a computerized database of up-to-date PIs, as discussed above, should be implemented as part of this education initiative.

- The FDA, in collaboration with physician organizations, should work with major medical journals and medical society web site editors to identify standard places for the dissemination of important new risk information about drugs and biological products.

- "Dear Doctor" letters should be disseminated by mechanisms other than hard-copy mail. Alternative mechanisms should include publication in medical journals (possibly as paid advertisements), placement on medical society web sites, and transmission to individual physicians by blast fax, blast email, and direct daily downloads to personal digital assistants (PDAs). Unlike letters, electronic transmission is inexpensive, timely, and repeatable. Thus, important risk information can be reinforced by more than one transmission.

- The content and format of "Dear Doctor" letters should be changed to emphasize the need for action by the prescribing physician. For example, a "Dear Doctor" letter should contain a bold-faced opening paragraph that emphasizes the possible severe outcome (e.g., permanent harm or death) to patients from the new adverse event, that the adverse event is probably preventable if the drug is used appropriately, and what necessary steps the physician must take to prescribe the drug appropriately.

- Pharmaceutical companies should be obliged to train and send their sales forces to physicians to educate them on important new risk information about company products. The company should provide incentives to sales representatives to do this because the highest priority of any company should be to prevent harm to patients who use their products. The effectiveness of the 80,000 pharmaceutical sales representatives in the United States in promoting the benefits of their companies' products is well documented, and they could have similar success in educating physicians about important product risks.

- New information technologies, such as computerized physician order entry (CPOE), offer enormous opportunities to communicate important risk information about drug and biological products. CPOE systems with well-designed decision support programs potentially could communicate important new risk information to physicians at the point of prescribing, i.e., at a time when the information is most needed. As these new information technologies become integrated into physician practice, the FDA, the pharmaceutical industry, and physician organizations should work with database providers and software vendors to incorporate the appropriate risk information into these electronic systems.

- The AMA encourages the FDA and the pharmaceutical industry to work with physician organizations to optimize physician education about the risks of drug and biological products through identification and implementation of effective methods of risk communication. The AMA also recommends that the Centers for Education and Research on Therapeutics (CERTs) program be charged with developing a research agenda in risk communication to help identify new and effective educational strategies.

Level 3 and Level 4 RMPs should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

The AMA has concerns about many of the tools that the FDA has proposed under Level 3 and Level 4 RMPs including:

- prescribing only by registered physicians (restricted distribution);
- certification programs for physicians;
- enrollment of physicians in a safety program;
- specialized systems or records that attest to safety measures having been satisfied (e.g., stickers, physician attestation of capabilities);
- dispensing only to patients with evidence or other documentation of safe use conditions (e.g., lab test results) (restricted distribution); and
- patient agreements/informed consent.

As discussed above, the AMA has general concerns about the FDA and product sponsors managing or restricting physician prescribing. There also are a number of other reasons why the AMA believes that Level 3 and Level 4 RMPs should be used only as a last resort to ensure that high-risk products with unique and important benefits remain on the market. These reasons include:

- While Level 3 and Level 4 RMPs may reduce risk, such programs most likely will also reduce access. Some patients who would benefit from a product subject to a high-level RMP may not be prescribed that product because of the added burdens on the prescriber.

- A less effective, less studied, and even less safe alternative drug or biological product not subject to a high-level RMP may be prescribed instead of a product with

a Level 3 or Level 4 RMP. There is some anecdotal information to suggest that this may be happening with drugs used to treat cardiac arrhythmias. Sotalol and quinidine, neither subject to an RMP, may be prescribed instead of dofetilide, which is subject to a high-level RMP, when dofetilide is actually the preferred drug.

- Level 3 and Level 4 RMPs that employ multiple tools are complex and may be confusing to both the physician and patient. This could result in unintended medication errors unrelated to adherence to the RMP. This could be magnified in patients with multiple diseases who are on multiple drug products with multiple high-level RMPs, all of which could be different.

- Many of the tools for Level 3 and Level 4 RMPs are administrative burdens for physicians. Therefore, unless the product provides a truly innovative therapy for a particular disease or for a specific subset of patients with a disease, it is unlikely that physicians will take the necessary time to prescribe the product.

- It is unclear what the impact of Level 3 and Level 4 RMPs will have on pharmaceutical company research and development plans. It is possible that a company could cease development of a promising drug because of the likelihood of a high-level RMP. High-level RMPs could have an adverse effect on pharmaceutical innovation, which would ultimately limit new drug discoveries.

- For certain drugs subject to Level 3 and Level 4 RMPs, patients may seek these products from alternative sources, such as illegal foreign Internet sites. For example, if a patient knows about the product but cannot find it easy to obtain in the United States, then the patient may take direct action and purchase the drug illegally. Also, a patient may be concerned about his or her privacy and want to avoid a high-level RMP that mandates patient registration with a pharmaceutical company.

For all of these reasons, the AMA believes the FDA must be highly discriminating in requiring a drug or biological product to have a Level 3 or Level 4 RMP. The serious nature of the risk must clearly be validated. As discussed earlier, objective criteria, agreed to by all stakeholders, should be developed to determine the need for such a high-level RMP. In addition, the FDA and the company must take great care in selecting the tools that will be employed in the RMP. Only the minimum number of tools needed to effectively reduce the risk should be employed in the RMP. Only those tools that have been shown to be effective in reducing the risk should be used, and the tools should be acceptable to other stakeholders (e.g., physicians).

An Integrated, Systems-Based Approach to Risk Management of Drug and Biological Products is Preferred to Product-Specific RMPs.

As discussed above, the decision to develop a RMP for a particular product, and the level of the RMP, needs to be determined on a case-by-case basis using objective criteria. On the other hand, the RMPs for any given level of risk should be as uniform as possible across products. This is especially the case for Level 3 and Level 4 RMPs.

Currently, the FDA uses a product-by-product approach in developing an RMP. Thus, every product has its unique RMP. For high-level RMPs, which often employ multiple tools, this results in a number of complex, administratively burdensome, and, in some cases, conflicting RMPs. As discussed above, this can be confusing to both physicians and patients and potentially could result in unintended medication errors.

Furthermore, it is unclear to the AMA whether any of the different Level 3 or Level 4 RMPs for currently marketed drug products, or the tools used in these high-level RMPs, have been thoroughly evaluated for effectiveness. The AMA requests the FDA to be forthcoming with any information about the effectiveness of current RMPs. The AMA also questions the impact on patient care of certain tools, such as requiring stickers to be placed on handwritten prescriptions, when physicians or hospitals no longer use paper prescriptions.

The AMA encourages the FDA, in collaboration with the pharmaceutical industry and other stakeholders (e.g., physician organizations), to take a more systems-based approach to risk management programs. Appropriate tools should be prospectively developed based on evidence of effectiveness, and a standard set of tools for each level of risk should be part of a standard “toolbox” of risk management tools. When a product meets the criteria for a RMP at a certain level, to the extent possible, a standard set of tools should be employed in that product’s RMP. At a minimum, any given tool should be consistent across products.

The AMA also believes that the FDA, the CERTs program, the pharmaceutical industry, physician organizations, and other stakeholders need to consider the incorporation of risk management for drug and biological products into more global quality assurance programs. As electronic medical records (EMRs) and CPOE become more common and they are electronically linked to other aspects of care (e.g. lab

test results), it should be possible to effectively incorporate drug risk management, as part of overall quality assurance, into the normal routine of physician practice. As an analogy, the Physician Consortium for Performance Measurement, convened by the AMA, is currently developing physician performance measures derived from evidence-based practice guidelines. The AMA is working with physician group practices that have EMRs to incorporate the performance measures into their systems so that satisfying the performance criteria becomes a routine part of medical practice.

SECTION V: HOW AND WHEN CAN RISK MANAGEMENT PROGRAMS BE EVALUATED?

The AMA strongly supports the evaluation of RMPs for effectiveness. In particular, we support the FDA's intent to require risk management tools to be pretested prior to their implementation in an RMP. As part of this pretesting, the FDA and the sponsor should seek the input of physicians and other affected stakeholders to see if the particular tool is acceptable. The AMA strongly concurs with the FDA that any RMP also must be evaluated after implementation to determine whether the program has met its desired objectives. As an important first step and as discussed above, the AMA believes that the FDA and the relevant sponsors of drug products with high-level RMPs currently should evaluate those RMPs, and the tools used in the RMPs, for effectiveness.

The AMA concurs with the FDA's view that metrics which capture actual health outcome data are preferred to those that measure a surrogate event or a process. Metrics, preferably quantitative, should be well-defined and validated. The AMA agrees with the FDA that two different and complementary evaluation methods should be used for key RMP goals or objectives. The AMA shares the FDA's view that spontaneous adverse event data should not be used as an outcome measure for RMP evaluation. The AMA also agrees with the FDA about the limitations of administrative claims data for evaluation of RMPs.

SUMMARY COMMENTS ON CONCEPT PAPER, RISK MANAGEMENT PROGRAMS

In summary, the AMA shares a common goal with the FDA to optimize the benefit/risk balance of drug therapy and to minimize the risks of drug and biological products. The AMA concurs with the FDA that the PI, combined with postmarketing surveillance, should constitute the risk management plan for the vast majority of drug and biological products. The AMA urges the FDA to publish its final rule on the PI and to develop a computerized database of PIs that is publicly available.

The need for a RMP, and the level of the RMP, should be made on a case-by-case basis using objective criteria that need to be developed by the FDA, in collaboration with the pharmaceutical industry and physician organizations. The AMA believes that the vast majority of drug or biological products that require an RMP should fall into Level 2. Again, the AMA supports a collaborative effort among the FDA, the pharmaceutical industry, and physician organizations to optimize physician education about the risks of drug and biological products through identification and implementation of effective methods of risk communication.

The AMA has a number of concerns about Level 3 and Level 4 RMPs and recommends that these high-level RMPs be used only as a last resort to keep high-risk products with unique and important benefits on the market. There needs to be a clear documented need for a high-level RMP that is based on objective criteria. Furthermore, the FDA is encouraged to use an integrated, systems-based approach to these high-level risk management programs to make them more uniform and less intrusive to physicians. While evaluation of the effectiveness of RMPs, and of their risk management tools, is recommended for all levels of RMPs, this is especially important for Level 3 and Level 4 RMPs.

The AMA also is concerned that the FDA and drug sponsors may be attempting to regulate the practice of medicine through some of the tools proposed for these high-level risk management programs. It has been long established that the FDA is not authorized to control the practice of medicine. *American Pharmaceutical Association vs. Weinberger* 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff'd sub nom. APhA v. Mathews* 530 F.2d 1054 (D.C. Cir 1976).

HOW CAN THE QUALITY OF SPONTANEOUSLY REPORTED CASE REPORTS BE IMPROVED? (FROM FDA CONCEPT PAPER, RISK ASSESSMENT OF OBSERVATIONAL DATA: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT)

Spontaneous adverse event reports serve an important purpose in generating signals about serious adverse events that may be caused by drug and biological products. Because physicians are the group best able to observe and communicate information about adverse events, the AMA has had longstanding policy that physicians

have an obligation to inform the FDA or product sponsors about potential serious adverse events associated with drug and biological products.

For the above reasons, the AMA has been a proactive MedWatch partner since the program's inception. For example, the AMA was a co-sponsor of one of the first public meetings on MedWatch. Over the years, the AMA has also worked with the FDA to educate physicians about the importance of voluntary reporting, on what to report, about how to make a meaningful report, and how to cooperate fully with follow-up calls from sponsors or the FDA. The AMA reaffirms its commitment to the MedWatch program and stands ready to work with the FDA and the pharmaceutical industry to continue to educate physicians about the importance of spontaneous reporting.

CONCLUSION

In conclusion, the AMA appreciates the opportunity to comment on the FDA's risk management activities. We hope that our insight into the issues discussed in the Concept Papers proves helpful for the FDA, and we look forward to working with the Agency as it moves forward in this area.

Sincerely,

MICHAEL D. MAVES, M.D., MBA

STATEMENT OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS

The American Society of Health-System Pharmacists (ASHP) is pleased to present the United States Senate Health, Education, Labor and Pensions Committee with comments on an issue of grave importance—the safety of our drug supply. It is essential that the American public have confidence in our Nation's drug approval and monitoring systems' ability to maintain the integrity of our drug supply and protect patients' health.

For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 30,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students.

ASHP has long taken a leadership role in efforts to improve medication safety. Pharmacists are the health care professionals best educated and positioned to monitor the safe and appropriate use of medications, often serving as the final safety check before medications reach the patient. ASHP keeps health-system pharmacists informed of drug safety issues and helps them respond appropriately. ASHP publishes drug information both for health professionals and consumers, promotes evidence based medication use programs, disseminates FDA's MedWatch notices, and maintains a drug shortage Web site that informs and offers guidance to help pharmacists manage shortages.

In recent years, drug safety and the FDA approval and monitoring process have come under intense scrutiny. With many important new drugs entering the market each year, some of which have been fast-tracked through the approval process, FDA's ability to monitor safety has been questioned. The short duration and small number of participants in the clinical drug trials required for FDA-approval dictates that the toxicity of new products cannot be fully understood when a drug is approved and initially marketed. FDA's postmarketing surveillance, therefore, needs to be modernized and strengthened to provide ongoing assessment of products on the market. Moreover, the FDA needs sufficient resources to fully implement the depth of programs necessary to prevent injury and save lives.

The FDA faces a difficult challenge—establishing a system of drug approval and monitoring that maintains a balance between the benefits of bringing a new, potentially life-saving drug to market quickly, and the risks associated with widespread use of a new drug.

This testimony will walk through the drug approval and monitoring process, examining opportunities to improve safety, while maintaining this important balance.

ISSUES RELATED TO THE FDA DRUG APPROVAL PROCESS

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the FDA is responsible for ensuring that all new drugs are safe and effective. Before any drug is approved for marketing in the United States, the FDA must make a determination that the drug is safe and effective for the conditions of use in the drug's labeling and that the benefits of approval outweigh the drug's risks.

According to a report by the Inspector General, new drug reviewers in the FDA's Center for Drug Evaluation and Research (CDER) have experienced shorter approval times and increased pressures to recommend approval of a drug even if they have reservations about the drug's safety or efficacy.¹ This pressure is illustrative of the need to better educate the American public about both the risks and the benefits of new drugs. It also highlights the potential conflict that arises by having FDA funding for the drug approval process relying heavily on user fees.

ISSUES RELATED TO POSTMARKETING SURVEILLANCE

Regardless of the rigor of the premarket drug approval process, postmarketing surveillance is essential to ensuring drug safety. The more widespread, longer-term use of a product in the real world detects adverse effects that often go undetected during clinical trials.

ASHP is pleased that on February 15, 2005, the FDA announced a plan to improve the way the FDA manages drug safety information to make FDA's review and decision-making processes more independent and transparent. However, it is important to review FDA's authority to monitor and examine drugs once they are on the market to ensure the FDA has sufficient authority to develop an enhanced post-marketing surveillance system necessary to meet today's needs.

Adverse Event Reporting Must be Encouraged. FDA's MedWatch program, which provides for the reporting of adverse drug events, is essential to detecting enhanced risk associated with medications. ASHP, through its Web site, coordinates an effort to provide this information in a timely manner to the pharmacy community. However, the MedWatch program must be strengthened to encourage more reporting. The information gathered from the MedWatch program must be acted upon in a timely manner, by someone separate from the team that initially approved the drug for marketing. Information must also be made available to patients and providers in a timely manner. This may require the FDA being granted additional authority to make labeling changes.

Authority Needed to Require Certain Postmarketing Safety Studies. The FDA's ability to measure the ultimate safety of a drug once it has entered the market is limited by the fact that the FDA cannot conduct independent clinical trials, and it is unclear whether the FDA can require manufacturers to conduct such studies. In order for the FDA to fully understand side effects of an approved drug that may not have surfaced in the limited premarket test group, it is essential that the FDA be able to require these studies under certain circumstances.

Funding Needed for Postmarketing Clinical Effectiveness Studies. There is also a significant need for studies comparing the clinical effectiveness of medications on the market. Pharmacists, other members of the health care team, patients, and private and public payers need objective, authoritative, and reliable evidence in order to make the best treatment decisions. Such research will contribute to the practice of evidence-based patient care, good clinical decision-making, and rational drug use. Since prescription drugs represent a significant portion of health care costs, the need for such research is increasingly important. Only the Federal Government has the ability to support such independent comparative research, provide oversight to safeguard the integrity of the research process, and disseminate the findings.

We encourage committee members to support expanded funding for the Agency for Healthcare Research and Quality (AHRQ) to sponsor this type of research. Impartial private sector entities could supplement the efforts of AHRQ, but the Federal Government needs to take the lead.

Clinical Trials Should be Disclosed in National Registry. While expanded FDA authority to require postmarketing clinical trials is an important start to building a stronger drug monitoring system, it will have limited impact if this information is not made available to the FDA and the public in some way. Disclosure is essential to creating a system of transparency and accountability necessary to promote consumer confidence.

ASHP supports the establishment of a mandatory registry established and administered by the Department of Health and Human Services. This registry should build upon the existing registry administered by the National Institutes of Health for clinical trials dealing with the effectiveness of treatments for serious and life-threatening conditions, and it should cover all publicly and privately funded clinical trials.

¹ FDA's Review Process for New Drug Applications: A Management Review, Inspector General Report March 2003. (OEI-01-01-00590)

All clinical trials undertaken, but not yet completed, should be added to the registry and, upon completion, the results should be posted as quickly as possible after FDA approval but before marketing commences. Strong enforcement mechanisms are necessary to ensure compliance.

Any opposition raised regarding the disclosure of a company's research action plan is outweighed by the public and individual patient's right to know and critically examine all available studies and their results.

Additional FDA Funding Needed for Postmarketing Surveillance. Additional funding is needed by the FDA, particularly in the area of postmarketing surveillance. Due to the fact that the Prescription Drug User Fee Act (PDUFA) requires manufacturers to pay a user fee when they submit a drug approval application, more resources are available for drug approval review than for postmarketing monitoring.

Such funding is necessary in order for the FDA to conduct postmarketing surveillance and establish a national clinical trial registry.

OTHER INITIATIVES ESSENTIAL TO IMPROVING DRUG SAFETY

Legislation Needed to Encourage Medical Errors Reporting. Legislation is needed to help create a culture of safety that would entice individuals to report medical errors and "near misses." The Senate passed legislation last year, the Patient Safety and Quality Improvement Act (S. 720), that would establish a system for reporting and analyzing errors reports and establish peer review protections for individuals reporting to the system. ASHP is encouraged that the committee plans to move that legislation forward this year.

Congress Should Consider a New Category of Drugs to Help Balance Safety and Access Concerns. There is a significant push to make more products available over-the-counter. In order to balance access with safety concerns, the Congress should consider making the appropriate changes in Federal statutes and regulations to establish an intermediate category of drug products that do not require a prescription but are available only from pharmacists and licensed health care professionals who are authorized to prescribe medications.

Pharmacists, who have the education, training, and expertise to help patients make appropriate therapeutic decisions, would be able to provide drugs in this new category directly to patients without a prescription, on the basis of appropriate assessment and professional consultation. This would enhance patient access, while addressing safety concerns that prevent drugs from being dispensed over the counter.

Current Drug Importation Laws Should be Enforced Vigorously Until a System Can be Established to Maintain Current FDA Assurance of the Safety and Authenticity. Working outside of the FDA's regulatory framework to import drugs from other countries is counterproductive to efforts to strengthen FDA's drug approval and monitoring processes. Current importation efforts increase the risk that Americans will receive drugs that do not meet the FDA's standards and are harmed as a result.

ASHP believes that current laws and regulations related to importation should be upheld and vigorously enforced until in order to (1) maintain the integrity of the pharmaceutical supply chain to avoid the introduction of counterfeit products into the United States; (2) provide for continued patient access to pharmacist review of all medications and preserves the patient-pharmacist-prescriber relationship; and (3) provide adequate patient counseling and education, particularly to patients taking multiple high-risk medications.

Before any consideration is given to opening the United States market to medications from abroad, systems should be put in place to guarantee the integrity of any new distribution networks. Related to this point, ASHP encourages stronger authority for the FDA and others to control the prescribing and dispensing of medications via the Internet. ASHP supports efforts that require pharmacy World Wide Web sites to list the States in which the pharmacy and pharmacists are licensed, and, if prescribing services are offered, requires that the sites (1) ensure that a legitimate patient-prescriber relationship exists (consistent with professional practice standards) and (2) list the States in which the prescribers are licensed.

FDA Should Be Given Broader Authority to Notify Providers of Drug Product Shortages. ASHP members and other health care providers have increasingly experienced drug shortages. These shortages not only affect access to care but, also due to the limited notice providers receive of impending shortages, increase the cost of alternative care and the likelihood of medication-related complications. ASHP strongly believes that the Congress and the FDA should consider expanding the definition of "medically necessary" drug products to enhance FDA's authority to require

pharmaceutical manufacturers to notify the appropriate government body well in advance of voluntarily discontinuing a product and put in place effective sanctions for manufacturers that do not comply with this mandate.

Direct-to-Consumer Advertising of Specific Drugs Should be Prohibited. Direct-to-Consumer (DTC) advertising has more than doubled over the last 5 years. Despite this dramatic expansion in advertising, FDA enforcement actions against ads that are in violation of FDA standards have dropped. While the FDA can require DTC ads to be scientifically accurate and provide a fair balance of risks and benefits, the FDA lacks the necessary resources to assure that companies comply.

ASHP is concerned about the impact DTC advertising for specific drug products has had on fostering inappropriate prescribing and supports a ban on such advertisements.

Drug Samples Should be More Carefully Regulated. ASHP also believes that addressing drug safety is incomplete without considering safety concerns that arise due to manufacturer samples that go through distribution channels that (1) do not foster pharmacist oversight of therapy, (2) result in poor drug control, allowing patients to receive improperly labeled and packaged, deteriorated, out-dated, and unrecorded drugs, (3) provide access to prescription drugs by unauthorized, untrained personnel, (4) may encourage inappropriate prescribing habits, or (5) may increase the cost of treatment for all patients.

FDA should be encouraged to provide the additional guidance necessary to ensure drug samples are distributed through channels meeting these criteria.

Manufacturers Should be Required to Make Available Unit Dose Packaging of Medications Commonly Dispensed in Hospital and Ambulatory Health Care Settings. ASHP urges the FDA to require manufacturers to provide all medications commonly used in hospitals and other ambulatory health care settings in ready-to-use unit dose packaging. The FDA issued a final regulation in February 2004 that requires pharmaceutical manufacturers to apply bar codes to "most prescription drugs" and "certain over-the-counter drugs that are commonly used in hospitals and dispensed pursuant to" a medication order. Currently, many drugs are not available from manufacturers packaged as a single dose ready for dispensing. In order for bar coding to have the greatest effect on patient safety, bar coded packaging of medications must be available at the unit-of-use level. Lack of availability of appropriate dosage forms packaged for unit dose dispensing places the burden on hospital pharmacy departments, who are not well situated to take on this role. In the interest of patient safety, manufacturers should be required to provide medications in dosage packaging commonly used in hospitals and ambulatory health system settings.

Concluding Comments. ASHP is encouraged by the reasoned approach the committee has taken to addressing drug safety concerns. The U.S. has a solid record for drug safety that should not be overlooked. The system, however, will benefit from a careful examination and enhancements to address current weaknesses. We look forward to working with the committee to develop balanced solutions to enhancing safe medication use and moving any necessary legislation forward.

PREPARED STATEMENT OF SENATOR GRASSLEY

Chairman Enzi, I congratulate you on becoming chairman of the Health, Education, Labor, and Pensions (HELP) Committee, and thank you for your leadership in holding hearings on the Food and Drug Administration (FDA) and drug safety. As you know, these issues have been a central concern of mine during the past year. My staff on the Finance Committee has been investigating serious allegations raised by whistleblowers that call into question whether the FDA is fulfilling its mission to protect the health and safety of Americans.

Indeed, the Food and Drug Administration has failed to put patient safety first with respect to both SSRIs and COX-2 drugs. Last November, the Finance Committee held an oversight hearing based on an investigation of the withdrawal of Vioxx, Merck's blockbuster COX-2 drug. Red flags had been raised about the safety risks of Vioxx before and after the drug had been approved by the FDA. The Vioxx hearing shed some much needed light on how the Food and Drug Administration regulated or rather failed to regulate Vioxx effectively.

The Finance Committee has a responsibility to more than 80 million Americans who receive health care coverage, including prescription drugs, under the Medicare and Medicaid programs. As Chairman of the Finance Committee, Merck's withdrawal of Vioxx was of particular interest because Medicaid paid over \$1 billion for Vioxx while it was on the market. Medicare and Medicaid beneficiaries rely on medicines paid for with federal funds. The Finance Committee has a responsibility

to make sure that every federal dollar paid for drugs is not misspent on unsafe drugs and drug companies who profit at the expense of consumer safety.

Historically, the Food and Drug Administration has met its charge to protect the health and safety of the American public. Those who work at the agency are, by and large, committed to doing no harm. Even so, the FDA has also stood watch over failures when it comes to drug safety this past year. Consequently, public confidence has been shaken.

When the FDA approves a drug, it's considered a Good Housekeeping seal of approval. Consumers should not have to second guess the safety of what's in their medicine cabinets. When the FDA approves a drug, Americans should be able to bank on its benefits outweighing its risks. If a drug presents an unacceptable risk, the FDA should take it off the market. This risk-benefit analysis should be non-negotiable. When it comes to putting patient safety first there is no room at the table for drug companies. The FDA should not be sitting down to negotiate with drug companies whose priorities too often appear to lie with their stockholders. A vital and pressing concern today is post-marketing surveillance and the way FDA monitors the safety of prescription drugs. Dr. Raymond Woolsey, a witness at today's hearing, stated in a Frontline interview in November 2003 that "the number of people hired at the [FDA] to protect, to analyze data and drug safety, is criminal. . . The teams that are needed to do drug safety are infinitely more than what they've got right now. We don't have a safety system in this country."

One of my concerns is that the FDA has a relationship with drug companies that is far too cozy. That's exactly the opposite of what it should be. Despite findings from a Merck study that heart attacks were five times higher for Vioxx patients than for patients on another drug, nearly two years passed before label changes were made by the FDA. Consumers and doctors remained largely unaware of the cardiovascular risks while Merck continued to aggressively market Vioxx during that time. The overriding concern of the FDA should have been the health and safety of the American people.

Evaluating drug safety, of course, involves balancing the risks against the benefits of each drug, and Vioxx is no different, but we need to know what the risks are in order to make those risk-benefit calculations. And in the case of Vioxx, doctors and patients did not have that opportunity. What I also find disturbing is that Merck negotiated with the FDA to place information about the cardiovascular risks of Vioxx in the "Precautions" section of the label rather than prominently displaying it as a "Warning."

Several witnesses at the Finance Committee's November hearing believed the FDA should have required a black box warning for Vioxx, the strongest label warning the FDA requires. FDA's own advisory committees recently agreed. Less than two weeks ago, the FDA joint advisory committee recommended black box warnings on all COX-2 labels.

FDA has also disregarded and downplayed important concerns and warnings from its own best scientists. We saw evidence of that in the way FDA treated Dr. Andrew Mosholder's findings on SSRIs and Dr. David Graham's findings on Vioxx. The FDA even attempted to undermine the publication of Dr. Graham's findings in *The Lancet*. According to Dr. Graham's peer reviewed and published findings, an estimated 88,000-140,000 excess cases of serious coronary heart disease are attributable to Vioxx, with about half these cases being fatal. That means there may be as many deaths attributable to Vioxx as the number of soldiers who died during the Vietnam War. Information about the Vioxx disaster needs to be shared with the public and shared in a timely manner.

This week I introduced the Fair Access to Clinical Trials Act of 2005 with Senator Dodd. I introduced this legislation as part of a sustained effort to restore public confidence in the federal government's food and drug safety agency. The FACT Act would expand www.clinicaltrials.gov to create a publicly accessible national data bank of clinical trial information comprised of a clinical trial registry and a clinical trial results database. Enactment of this bill would be a meaningful step toward greater transparency and accountability in clinical trials and the scientific process.

In addition, Senator Dodd and I are working on a bill to establish an independent office for drug safety within the FDA. The independence of the office would not exist solely on an organizational chart. The office would have an independent director and regulatory authority. When it comes to drug safety, intra-agency community is indeed essential. However, the Office of New Drugs is hampered by real and perceived conflicts of interest. An independent drug safety office would more effectively regulate drugs post market. It doesn't make sense, from an accountability standpoint, to have the office that reviews the safety of drugs that are already on the market to be under the thumb of the office that puts the drugs on the market in the first place.

As I continue with my Constitutional duties to conduct oversight as Chairman of the Finance Committee, I look forward to working closely with you, Mr. Chairman, to ensure that critical changes are made within the FDA to keep the agency focused on its mission to protect public health and safety. I look to your leadership and seek your support with the legislation that is necessary to help get FDA back on the right track. Again, I commend you for holding these hearings and look forward to working with you.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY JANET WOODCOCK, M.D.

Hon. MIKE ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510-6300.

DEAR CHAIRMAN ENZI: Thank you for the facsimiles dated March 21, 2005, including questions for the record related to the Committee's recent hearings, March 1 and 3, 2005, entitled, "FDA's Drug Approval Process: Up to the Challenge?" We have repeated your questions below, followed by the Food and Drug Administration's (FDA or the Agency) response.

Question 1. Some witnesses at our Tuesday hearing emphasized that clinical trials, because of their size and length, cannot always predict fully the potential side effects of a drug. Would you explain this in more detail?

Answer 1. The most recent actions concerning the drug Vioxx (rofecoxib) illustrate the vital importance of the ongoing assessment of the safety of a product once it is in widespread use. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective for a given indication. Experience has shown that the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness. A new drug application (NDA) typically includes safety data on several hundred to several thousand patients. If a serious adverse event occurs in 1 in 5,000 or even 1 in 1,000 users, it might not occur in clinical trials of this size. When the drug is used by many times that number of patients, that event could show up as a serious risk. Occasionally, serious adverse effects are identified after approval either in post-marketing clinical trials or through spontaneous reporting of adverse events. That is why Congress has supported, and FDA has created, a strong post-market drug safety program designed to assess adverse events identified after approval for all of the medical products it regulates as a complement to the pre-market safety reviews required for approval of prescription drugs in the United States.

Question 2. What technologies and processes are currently available to predict potential adverse events during drug development and/or identify post-marketing safety issues?

Answer 2. During the Pre-Market Phase, ODS works with OND at pre-NDA and pre-Biologics Licensing Applications (BLA) meetings with industry to review safety information and to discuss proposed risk management plans and the need for any post-approval risk management studies. During NDA and BLA review, ODS and OND work together in the development and review of risk management programs. ODS provides expertise in the review of proposed proprietary drug names, labeling, and packaging to minimize medication errors, patient labeling and Medication Guides, and Phase 4 safety studies. ODS staff are involved in the preparation for and may present information at advisory committee meetings involving safety issues and risk management for pending applications and when post-marketing safety information is available for similar products.

Under Title 21, Code of Federal Regulations (CFR) 314.80, Post-Marketing Reporting of Adverse Drug Experiences, subsections (b) (review of adverse drug experiences) and (c) (reporting requirements), manufacturers are required to review and report to FDA all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic. This includes information derived from commercial marketing experience, post-marketing clinical investigations, post-marketing epidemiological/ surveillance studies, and reports in the scientific literature and unpublished scientific papers. There is comparable language in 21 CFR 600.80 for biologics.

FDA recently published a proposed rule that would require drug manufacturers to submit reports electronically. The rule, if finalized, would help harmonize world-

wide reporting of post-marketing safety information and expedite detection of safety problems for marketed drugs. The Agency is also expanding the reporting requirements for manufacturers of biological products to include adverse event reports from unlicensed blood banks and transfusion services.

In concert with industry's reporting requirements, the Food and Drug Administration Modernization Act of 1997 (FDAMA) requires sponsors of approved drugs and biological products report to FDA annually on the progress of their post-marketing study commitments, both those that are required and those that are agreed upon in writing. Under FDAMA, FDA is obligated to track the progress of post-marketing study commitments, make certain information about commitments available to the public, and to report annually in the *Federal Register* on the performance of post-marketing study commitments (PMC). This tracking and reporting allows for FDA to monitor compliance of PMCs. The status of PMCs is published on the CDER website at <http://www.fda.gov/cder/pmc/default.htm>.

During the Post-Market Phase, one of ODS' primary roles is to provide expertise in the review of post-marketing safety data and to maintain and coordinate CDER's post-marketing surveillance and risk assessment program. This program includes the Adverse Event Reporting System (AERS), a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. Information in AERS comes from required reporting by companies and through voluntary reports submitted directly to FDA's MedWatch program by consumers and health professionals, which together total more than 350,000 reports per year. ODS review of AERS data may provide signals of safety issues that did not appear during the drug development process as well as those that appear more frequently or with a greater degree of severity after approval than was seen in clinical trials. ODS review of AERS reports may also detect product quality problems that are referred to the Office of Compliance.

Individual reports may trigger further evaluation of similar reports in the AERS database and could signal important safety concerns prompting regulatory actions both in the U.S. and abroad. To further investigate safety signals, ODS safety evaluators, epidemiologists and drug utilization specialists perform research to define drug use, background rates of the event in the treated population, and epidemiological trends.

In addition to AERS, ODS staff are responsible for the acquisition, analysis, and interpretation of information from contracted databases on drug use in various populations, including in-patients, children, and patients over time that help place safety signals into context and inform regulatory decision-making. For newly approved products with important safety concerns, ODS independently evaluates product utilization to evaluate whether these products are being used in a safe manner and works collaboratively and pro-actively with OND and industry on related issues.

ODS' cooperative agreement program in pharmacoepidemiology provides CDER with access to external experts with access to population-based databases for the purpose of studying important post-marketing drug safety questions. CDER works collaboratively with the cooperative agreement partners to identify research areas and to design and conduct studies to investigate suspected associations between specific drug exposures and specific adverse events and to estimate risk. FDA is revising this program to use contracts, rather than cooperative agreements, to help focus on drug safety issues that are of the highest priority and urgency to the Agency.

ODS also uses additional data sources as needed, such as the National Electronic Injury Surveillance System: All Injury Program (NEISS-AIP), an ongoing active surveillance system for the purpose of collecting data on all injuries presented to a probability sample of U.S. hospital emergency departments; the Drug Abuse Warning Network, a public health surveillance system that monitors drug-related visits to hospital emergency departments and drug-related deaths investigated by medical examiners and coroners.

ODS reviews reports of medication errors that have occurred with marketed products and recommends changes to product names, labeling, and/or packaging to prevent future errors. ODS works with OND and the Office of Generic Drugs to review risk management programs for approved products to assess their implementation and effectiveness. ODS reviews patient labeling and Medication Guides that are put in place to address serious and significant public health concerns both pre-marketing and when issues arise after a product is marketed. ODS assists the Office of Training and Communication in the development of Consumer Drug Information Sheets by assessing readability.

ODS' MedWatch program is an important tool in both acquiring and disseminating safety information. In addition to receiving direct reports of serious adverse events and problems related to drugs and other medical products regulated by FDA from consumers and health professionals, the MedWatch program also provides im-

portant and timely clinical information on safety issues involving medical products, including prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products (e.g., medical foods, dietary supplements and infant formulas). Medical product safety alerts, recalls, withdrawals, and important labeling changes that may affect the health of all Americans are disseminated to the medical community and the general public via the MedWatch website and the MedWatch E-list that provides e-mail updates to over 46,000 subscribers. MedWatch Partners are over 150 health care professional organizations, consumer groups, and web-media groups that work with FDA to help keep their members informed about medical product safety information and reporting. Partners are encouraged to play an active role in post-marketing surveillance.

FDA created an independent Drug Safety Oversight Board (DSB or the Board) to enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety. The DSB will oversee the management of important drug safety issues within the CDER. The DSB will be comprised of members from FDA and medical experts from other HHS agencies and government departments (e.g., Department of Veterans Affairs). The Board also will consult with other medical experts and representatives of patient and consumer groups. CDER's Manual of Policies and Procedures has been updated to reflect the organization of the DSB; you may view this document by visiting: <http://www.fda.gov/cder/mapp/4151-3.pdf>.

FDA recently asked the Institute of Medicine (IOM) to look at the structure of our post-marketing surveillance program and to give FDA their expert advice on whether additional changes are needed to the Agency's approach to drug safety, which could include recommendations for changes in the CDER's organizational structure.

RESPONSE TO QUESTIONS OF SENATOR HATCH BY JANET WOODCOCK, M.D.

Question 1. I believe it is important for the FDA to look for ways to address differences of opinion within the agency. I think that [when] FDA officials have conflicting messages about the safety of specific drugs, it is extremely confusing to the general public. How would this program address disagreements among FDA scientists regarding the safety of a specific drug? Would this program have the FDA speak with one voice or would the public be given the opportunity to review the concerns of all FDA scientists? How would the new independent Drug Safety Oversight Board interact with the individuals involved with this program?

Answer 1. In November 2004, Dr. Crawford announced that CDER was establishing a new "Differing Professional Opinions and Dispute Resolution" Program. For more information about this program, please visit: <http://www.fda.gov/bbs/topics/news/2004/new01131.html>. CDER has developed a Manual of Policies and Procedures describing how this dispute resolution process will be managed. This process is available to any individuals in the Center who wish to express their differing professional opinions (DPOs) concerning any regulatory actions or policy decisions with significant public health impacts in instances when the normal procedures for resolving internal disputes are not sufficient.

In most cases, free and open discussion of scientific issues among review teams, and with supervisors, managers, and external advisors leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact. That is why CDER's new program provides for a review of the involved differing professional opinions by FDA and outside experts. An *ad hoc* panel, whose members were not directly involved in the disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

In addition to this program for resolving individual disputes regarding any regulatory matters or policies, CDER is establishing the Drug Safety Oversight Board (DSB) to specifically address drug safety issues and to assist in the resolution of disputes and differing professional opinions between staff from the Office of New Drugs and the Office of Drug Safety within the Center for Drugs. The membership of the Board has been carefully balanced with equal representation from both the Office of New Drugs and the Office of Drug Safety, along with representatives from other offices within CDER, the Center for Biologic Evaluation and Research, the Center for Devices and Radiological Health, the National Cancer Institute and the Department of Veterans Affairs. These organizational disputes will be addressed during meetings of the Board, with a final recommendation reached through achievement of consensus or through voting of the Board if no consensus can be reached.

Question 2. I commend the FDA on its willingness to increase communication with the public on drug safety. I believe that will make a significant difference for both physicians and their patients when they are making treatment decisions. Besides the internet, how will this information be provided to the public so they may be able to access information about pharmaceutical products?

Answer 2. As part of the vision announced on February 15, 2005, by the Department of Health and Human Service's Secretary Leavitt and FDA's Acting Commissioner Crawford, FDA will create a new independent DSB to oversee the management of drug safety issues. The Agency plans to improve transparency by providing emerging information to health providers and patients about the risks and benefits of medicines.

We understand that many Americans still do not have access to the Internet and that Internet communication is just one form of communication. In addition to using the Internet as a communication medium, FDA also uses trade and other press as well as other forms of external communication to convey safety information. We routinely use print media (periodicals) and coordinate with the press to publicize information. We will continue to use magazine advertisements, press releases, and other campaigns to inform the public.

FDA uses a very important means of communication, FDA-approved patient labeling, which includes:

Patient Package Inserts. For some prescription medicines, FDA approves special patient materials to instruct patients about the safe use of the product. These materials may be given to patients by their health care provider or pharmacist, and are considered part of FDA-regulated product labeling.

Medication Guides. FDA may require distribution of Medication Guides, FDA-approved patient information, for selected prescription drugs that pose a serious and significant public health concern. Medication Guides will be required if FDA determines that one or more of the following circumstances exist:

Patient labeling could help prevent serious adverse effects;

The drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product;

The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

In addition, FDA will be creating a Drug Watch Web Page, which will include emerging information for both previously and newly approved drugs about possible serious side effects or other safety risks that have the potential to alter the benefit/risk analysis of a drug, affect patient selection or monitoring decisions, or that can be avoided through measures taken to prevent or mitigate harm. FDA has recently issued a draft guidance entitled; "FDA's 'Drug Watch' for Emerging Drug Safety Information," which articulates the Agency's current thinking on the topic. This draft guidance is open for public comment and may be viewed by visiting: <http://www.fda.gov/cder/guidance/6657dft.pdf>. Other new communication channels will also include:

Health care Professional Information Sheets. One-page information sheets for health care professionals for all drugs on FDA's Drug Watch and all drugs with Medication Guides (FDA-approved patient labeling) containing the most important new information for safe and effective product use, such as known and potential safety issues based on reports of adverse events, new information that may affect prescribing of the drug, and the approved indications and benefits of the drug.

Patient Information Sheets. One-page information sheets for patients containing new safety information as well as basic information about how to use the drug in a consumer friendly format for all products on Drug Watch.

All of this information will be provided on the Internet.

RESPONSE TO QUESTIONS OF SENATOR GREGG BY JANET WOODCOCK, M.D.

Question 1. During the hearings, when questioned about whether the FDA needed additional authority to require label or labeling changes on prescription drug products it appeared that Dr. Sandra Kweder and Dr. Janet Woodcock—the FDA witnesses at each of the hearings—responded differently to the question. Does FDA have adequate authority for the drug approval and postmarket surveillance processes? Does FDA need any additional authority to require label or labeling changes on drug products, to require phase IV clinical trials, or to withdraw marketed drug products? Does FDA need any additional authority to ensure the safety and efficacy of new and marketed drugs?

Answer 1. We do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues. In most cases, FDA and the sponsor are able to reach agreement on the labeling text fairly quickly (a few weeks). As Dr. Janet Woodcock testified on March 3, 2005, a key factor in labeling changes is that once a label change is made, old labels in paper form are still in distribution and it takes time to get newer labels into circulation. Dr. Woodcock testified that the new strategy of posting drug safety information sooner using the Drug Watch mechanism will help alleviate that factor because it will enable FDA to get information directly to the people who need it in a timely manner.

In addition to the Drug Watch web page, our February 15, 2005, announcement included plans to create a new Drug Safety Oversight Board (DSB) to provide independent oversight and advice on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's website to health care professionals and patients. For more information on this initiative, please visit: <http://www.fda.gov/oc/factsheets/drugsafety.html>. Also, FDA is intensifying our current efforts to provide the public with the most important information for the safe and effective use of drugs in patient-friendly language. Two tools, Patient Information Sheets and Health care Information Sheets, will allow FDA to deliver emerging safety information to patients and health care providers.

To carry out these enhancements, the Agency's fiscal year 2006 budget request includes an increase of \$5 million for the Office of Drug Safety, bringing total funding to \$22.9 million (a nearly 25 percent increase).

Question 2. Concerning the recent withdrawal of marketed drugs, I understand that 12 of the 17 drugs taken off the market were used in ways that were unsafe. What drugs were they? How were they used? Was this use off-label? Did the companies involved withdraw the drug products from the market or did FDA require the withdrawals?

Answer 2. We are providing a list below of safety-based drug withdrawals associated with unsafe labeled or off-label use of the drug product. All of these products were voluntarily withdrawn by the manufacturer. Those drugs for which the company made the withdrawal decision independent of FDA advice are indicated with an asterisk. In all other cases, the decision was made jointly by FDA and the company or by the company upon FDA recommendation.

Propulsid (cisapride), a drug to treat gastroesophageal symptoms, was withdrawn in 2000. It was withdrawn due to adverse events associated with labeled, contraindicated usage (concomitant use of medications, which inhibit a certain metabolic pathway), which continued despite the fact that the label included a boxed warning about this interaction and several "Dear Healthcare Provider" letters were sent out to practicing physicians as reminders.

Lotronex (alosetron), a drug to treat Irritable Bowel Syndrome in women, was withdrawn in 2000 and reintroduced in 2002 under a restricted distribution program. Lotronex was withdrawn because of the occurrence of ischemic colitis in patients taking the drug, many of whom were prescribed the drug for unapproved indications.

Duract (bromphenac), a drug to treat acute pain, was withdrawn in 1998. The drug was found to have a very high rate of liver toxicity when used for longer than a few weeks. Despite several label changes, including a boxed warning and several "Dear Health Care Provider" letters advising use of the drug for no more than two weeks, cases of severe liver toxicity continued to be reported in patients taking the drug for prolonged periods.

Seldane (terfenadine), a drug to treat seasonal allergic rhinitis, withdrawn in 1998. Seldane caused an abnormal prolongation of heart electrical pathways when used in combination with other drugs that inhibited certain metabolic pathways. Despite a boxed warning and other measures to educate prescribers, reports of serious cardiovascular events, including death, continued due to Seldane and contraindicated concomitant medicines.

*Hismanal (astemizole), a drug to treat seasonal allergic rhinitis, was withdrawn in 1999. This drug was withdrawn under the same set of circumstances that Seldane had been several months before.

Mibefradil, a drug to lower blood pressure, was withdrawn in 1998 because it caused a potentially fatal heart rhythm disturbance when used in combination with some other drugs. Warnings and other notifications were not successful in mitigating such use.

Voluntarily withdrawn from the market by the manufacturer, but not due to use inconsistent with the label:

Bextra (valdecoxib), a drug to treat acute and chronic pain, was withdrawn in 2005. It was withdrawn due to post-marketing data regarding risk of CV safety associated with it and other anti-inflammatory drugs, and a very high rate of serious skin reactions that is not shared by other similar drugs.

*Vioxx (rofecoxib), a drug to treat acute and chronic pain, was withdrawn in 2004. It was withdrawn due to concerns of an increased risk of CV events.

Baycol (cerivastatin), a drug to treat high cholesterol, was withdrawn in 2001. It was withdrawn due to reports of rhabdomyolysis (severe and potentially serious muscle toxicity) that was found to be far more common with Baycol than other similar drugs.

*Raplon (rapacuronium), a drug used to induce anesthesia, was withdrawn in 2001 due to reports of serious bronchospasm associated with its use.

Phenylpropanolamine, a nasal decongestant, was withdrawn in 2000. Never approved by FDA, this very old drug was voluntarily removed from numerous prescription and non-prescription products by manufacturers, due to concerns that it might cause strokes.

Rezulin (troglitazone), a drug to treat diabetes, was withdrawn in 2000 at the time of introduction of newly approved products that could serve as less toxic, adequate substitutes. Rezulin included labeling warning of liver toxicity and the need for routine monitoring of patients. Several "Dear Healthcare Provider" letters about this toxicity and need for monitoring were issued.

*Rexar (grepafloxacin), an antibiotic, was withdrawn in 1999. It was withdrawn by the company after the manufacturer observed a small number of severe CV events.

Question 3. For several years, FDA has been implementing an initiative to make product labels easier to use by consumers. For example, FDA issued regulations to require that nonprescription drugs carry clear, simple and readable labeling. FDA took this action to make it easier for consumers to understand information about OTC drug products, including the benefits and risks, and how the drugs should be used most effectively. Does FDA intend to review prescription drug labeling to see if it is possible to make it easier for consumers and caregivers to find and understand important information about the products?

Answer 3. FDA agrees that the current package insert format is inadequate. Therefore, we have embarked on a major initiative to improve it. In recent years, there has been an increase in the length, detail and complexity of prescription drug labeling, making it harder for health care practitioners to find specific information and to discern the most critical information in product labeling. In the *Federal Register* of December 22, 2000, (65 FR 81082) FDA issued a proposed rule to revise its regulations governing the content and format of labeling for human prescription drug products. Prior to issuing the proposal, the Agency evaluated the usefulness of prescription drug labeling for its principal audience to determine whether, and how, its content and format could be improved. The Agency used focus groups, a national physician survey, a public meeting and written comments to develop multiple prototypes and to ascertain how prescription drug labeling is used by health care practitioners, what labeling information practitioners consider most important, and how practitioners believed labeling could be improved. The Agency developed a prototype based on this accumulated information as the model for the proposed rule. FDA received many comments on the proposed rule and is working to finalize it in the near future. Publication of this rule will be accompanied by publication of four implementing guidance documents.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY BY JANET WOODCOCK, M.D.

Question 1. In your testimony, you and Dr. Kweder described how the agency approves drugs under the statutory "safe and effective" standard, which the agency applies by comparing the known benefits of the drug against the known risks and assessing whether the benefits exceed the risks. Dr. Kweder and you explained, for example, how the agency assessed benefit with respect to the disease or condition to be treated, so that treating a tension headache, which goes away on its own and is in no sense life-threatening, is considered to offer considerably less benefit than treating a life-threatening cancer, and the risks that may be tolerable are considerably higher.

Under section 515 of the statute, the agency approves pre-market approval applications for medical devices if there is reasonable assurance of safety and effectiveness. Does application of this standard also involve comparing benefit and risk? If so, please explain how the application is similar to, and differs from, the risk-benefit

assessment that the agency performs for a drug? If not, why not? Please explain in detail, and with examples, how the agency applies the standard of reasonable assurance of safety and effectiveness.

Answer 1. FDA wants to emphasize that all drugs and devices, regardless of their approval mechanism, must have benefits that outweigh risks.

For devices going through the pre-market approval application process, there is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks (21 CFR 860.7(d)(1)). There is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results (21 CFR 860.7(e)(1)).

For devices, the mechanisms of assessing the benefits and the risks are analogous to drugs. Assurance of safety is based upon investigations using laboratory animals, investigations involving human subjects, and non-clinical investigations including *in vitro* studies (21 CFR 860.7(d)(2)). The valid scientific evidence to determine a reasonable assurance of effectiveness of a device shall consist principally of well controlled investigations (21 CFR 860.7(e)(2)). The device regulations also allow for the consideration of other types of studies as well (21 CFR 860.7(e)(2)).

The Center for Devices and Radiological Health (CDRH) similarly assesses benefit with respect to the disease or condition to be treated. For example, a device that uses shockwave therapy to treat a pain associated with tendonitis, which may be treated with physical therapy and is in no sense life-threatening, is considered to offer less benefit than devices used to treat a life-threatening condition, such as replacing a faulty heart valve. Further, the risks that would be considered acceptable will be higher in the latter case.

FDA's analysis of VIOXX was based on our assessment of the available data, the recommendations from the advisory committee, and our best judgment of the potential benefits of the drugs compared to the potential risks of the drug when used according to the recommendations included in the revised labeling.

Question 2a. In the VIGOR trial, compared with naproxen, Vioxx at 50 mg increased the risk of heart attacks by a factor of 5. At that dose, the approved indication was the short-term treatment of acute pain. Do these risk-benefit analyses still seem reasonable to you?

Answer 2a. FDA carefully considered all the CV findings from the VIGOR study, and available data from other trials, in assessing the impact of the VIGOR data on the continued safe use of the drug. FDA presented the results of the VIGOR study at a public Arthritis Advisory Committee meeting on February 8, 2001. The GI, CV, and general safety results of the VIGOR study were presented and discussed extensively. The expert panel, which included two cardiologists, recommended that both the positive GI information (reduced risk of serious gastrointestinal bleeding versus naproxen) as well as the potential increased risk of CV events (compared to naproxen) be included in the label. The panel did not recommend withdrawal of the 50 mg dose from the market.

Vioxx 50 mg was originally approved only for the short-term management of acute pain. Based on the data available to FDA at that time, we concluded that the potential risk of short-term use of VIOXX 50 mg did not outweigh the potential benefits. FDA did however, implement changes to the VIOXX labeling that specifically stated that the prolonged use of the 50 mg dose was not recommended and that the maximum recommended dose for prolonged use in osteoarthritis and rheumatoid arthritis was 25 mg daily.

FDA's analysis of VIOXX was based on our assessment of the available data, the recommendations from the advisory committee, and our best judgment of the potential benefits of the drugs compared to the potential risks of the drug when used according to the recommendations included in the revised labeling.

As you know, FDA convened a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committees in February 2005 to discuss overall benefit to risk considerations, including CV and GI safety concerns for COX-2 selective non-steroidal anti-inflammatory drugs. The Advisory Committees analyzed all available information from recent studies of Vioxx, Celebrex, Bextra, naproxen, and other data for non-selective NSAIDs and COX-2 selective products.

Following the joint meeting, FDA scientists conducted a thorough internal review of the available data regarding CV safety issued for COX-2 selective and non-selective

tive NSAIDs. It was determined that Bextra was associated with an approximately two-fold increased risk of serious CV events compared to placebo. On April 6, 2005, FDA completed a “Decision Memo—Analysis and Recommendations for Agency Action—COX-2 Selective and Non-Selective NSAIDs” based upon the internal review. The Decision Memo stated that, based upon detailed conclusions, the Agency should ask the manufacturer of Bextra, Pfizer Pharmaceuticals, to voluntarily remove Bextra from the U.S. market. Pfizer agreed to do so.

On April 7, 2005, FDA issued the enclosed Public Health Advisory, indicating that the Agency had asked Pfizer to voluntarily remove Bextra from the U.S. market. The Agency is also asking manufacturers of all marketed prescription NSAIDs, including Celebrex (celecoxib) to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of CV events and the well described, serious, potential life-threatening GI bleeding associated with their use.

Further, manufacturers of non-prescription (over-the-counter) NSAIDs are also being asked to revise their labeling to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment of these products in accordance with the package instructions. In addition, FDA advised the public to contact their health care providers to see if other marketed NSAIDs may be helpful in treating their pain. For more information on FDA’s recent actions, please visit: <http://www.fda.gov/cder/drug/infopage/COX2/default.htm>.

Question 2b. Some have attributed tens of thousands of deaths to the use of Vioxx. Dr. Kweder has described these deaths as “theoretical.” Dr. Galson said they were based on “junk science.” Does the agency stand by these statements?

Answer 2b. Dr. Kweder’s description of deaths as “theoretical” is a reference to epidemiological studies that project the numbers of deaths from adverse drug reactions. Epidemiology takes certain information that is received and attempts to apply that information to the entire population. Conclusions from this data are not conclusive, but are merely estimates. Any epidemiological study that says a million patients suffered adverse events is a theoretical estimation of the total adverse drug reactions that is derived by extrapolating the actual numbers observed to the population as a whole. Therefore, these can be considered “theoretical” deaths. The accuracy of projection is highly dependant on the accuracy of the information, methodology, and assumptions used in the study. While theoretical deaths are estimates and must be distinguished from confirmed deaths, this nevertheless provides valuable information about potential outcomes, and FDA takes this information very seriously in determining whether to revise the risk/benefit profile for a particular drug.

The “junk science” quote comes from a conversation with a Washington Post reporter that was taken out of context. The FDA official interviewed was asked to respond to the reporter’s question about whether it was accurate to state that a certain number of individuals in particular Congressional districts could be said to have died of cardiovascular events because of Vioxx. It is not possible to derive from risk estimates the cause of a particular individual’s death. This concept is complicated to explain, and FDA’s official reacted to it by characterizing the particular statement regarding deaths of individuals in a Congressional district as “junk science.”

Question 2c. Does the agency believe that Vioxx increases the risk of heart attack and stroke? If not, why not?

Answer 2c. Following the February 16–18, 2005, joint meeting of FDA’s Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, FDA scientists conducted an internal review, taking into consideration the recommendations of the Advisory Committees, of the available data regarding CV safety for COX-2 selective and non-selective NSAIDs. On April 6, 2005, FDA completed a document entitled, “Decision Memo—Analysis and Recommendations for Agency Action—COX-2 Selective and Non-Selective NSAIDs” (located at: <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>). The Decision Memo reflects the Agency’s evaluation of the risk/benefit profile of Vioxx, Celebrex, and Bextra, among others. The memo concluded that “these three approved COX-2 selective drugs are associated with an increased risk of serious CV events, at least at some dose, with reasonably prolonged use.”

Question 2d. If so, does the agency believe that some of the 20 million people who used Vioxx actually experienced heart attack or stroke because of Vioxx? If not, why not? If so, how many heart attacks and strokes does the agency believe Vioxx caused?

Answer 2d. Based on evidence from clinical trials, it is possible that some of the patients who were treated with Vioxx may have experienced a heart attack or stroke related to the use of Vioxx. We cannot reliably state how many heart attacks and strokes were caused by Vioxx alone, in part because the estimates vary depending on how you assume Vioxx was used and at what time point you believe the CV risks of Vioxx start.

In his presentation prepared for FDA's Advisory Committee meeting on NSAIDs in February 2005, Dr. Robert O'Neill described the many challenges and assumptions involved in making projections of harm associated with Vioxx to the general population that might have been exposed to Vioxx. To illustrate these challenges, he considered the types of assumptions, often unverifiable, that have to be made to make any projection. He illustrated an approach that emphasized the importance of when during exposure the risk occurs, what is its time pattern, and how many people are estimated to be chronically exposed for various durations. The clinical trials available were used for some estimates. The approach estimated the cumulative risk of confirmed thrombotic events, myocardial infarction (MI) and sudden death for Vioxx from two different clinical trials, VIGOR and APPROVe, trial designs of different duration, with different patient populations, with different doses, and with different control groups. He then estimated and projected to the population sizes that would typically have been exposed for different durations of chronic usage. For MI and sudden CV death, the projections for the 25mg and 50mg combined were between 32,418 to 33,093 people, depending upon assumptions. For confirmed thrombotic events occurring with 14 days of last study dose the projection were between 47,710 and 49,440. Taking all the known and unknown sources of variability as well as the statistical uncertainty in the data, the estimates could be larger or smaller.

Question 3a. Please explain how the agency's response to the VIGOR trial would have been different if Secretary Leavitt's recently announced independent board had been in place at the time? What actions would have occurred?

Answer 3a. FDA's experience with Vioxx and other recent drug safety events are the impetus behind our forming the Drug Safety Oversight Board. Had the Drug Safety Board existed at the time FDA became aware of the results of the VIGOR trial, we believe that CDER staff would have identified the trial results and concerns as an issue that would have warranted deliberation by the Board. It is difficult to speculate exactly what would have happened, but we feel that the Board as it is currently conceptually proposed would have made its best scientific judgments and recommendations based on all of the safety information available.

Question 3b. Is there reason to think its analysis of the VIGOR data and recommendations stemming from it would have been different from those of the FDA reviewers at the time? What authority would they have had to take corrective actions?

Answer 3b. Again, it is difficult to speculate what would have happened in this case had the Board existed at the time the VIGOR trial results became known. However, whatever recommendations the Board may have made would have been presented to the Center Director who would have made the final determination on how to proceed. It then would have been the responsibility of the appropriate CDER program offices to carry out the decision of the Center Director.

Question 3c. Does the agency believe that use of the drug would have been different? In particular, would significantly fewer people have experienced heart attack and stroke? If not, please explain why the recent FDA proposals are an adequate response to the Vioxx disaster.

Answer 3c. Again, it is difficult to speculate with confidence the level of influence the Drug Safety Oversight Board's involvement would have made in the VIOXX case. We are confident, however, that the actions that have been announced recently including the formation of the DSB, the introduction of the "Drug Watch," increased involvement of outside expertise, recent publication of risk management guidance, and other activities are an appropriate proactive response to the recent drug safety concerns. But we do not assume that these actions alone are adequate. We are continuing to proactively discuss and seek advice and feedback from internal and external sources on possible additional actions we can take. For example, we look forward to the Institute of Medicine's report on the drug safety system in the U.S.

While we would not characterize the Vioxx situation as a "disaster," we have openly conceded the fact that there is room for improvement in our post-marketing drug surveillance program and that is why we have acted quickly to improve our drug safety processes and our internal and external communication of drug safety issues. We agree that discussions with the company to change the labeling for Vioxx

were lengthy. However, in the future, we expect that the Drug Watch page will provide a forum for informing the public sooner about emerging safety issues.

Question 4. In January 2005, the data from an early clinical trial of Celebrex indicating an increased risk of cardiovascular problems were posted on a clinical registry database. The results from this trial had never before been released to the public. Were these results given to the FDA? When? In what form? Please explain in detail how the agency assessed these data. Were they ever reflected in the labeling of the drug? Did the agency do any sort of follow-up? Did this study play any role in the agency's assessment of the heightened cardiovascular risk from Vioxx shown by the VIGOR trial?

Answer 4. The sponsor gave these results to FDA. The report, submitted on June 7, 2001, indicated that a number of patients (n=13) who participated in the study had adverse events, which were listed using the WHO preferred term "cerebrovascular disorder." The Division of Neuropharmacological Drug Products (DNBP) requested narratives be submitted for all 13 patients. Upon review of the narratives all 13 appear to have unequivocally sustained either a stroke or transient ischemic attack during or within 28 days of the study's termination. The incidence of serious adverse events (including deaths), adverse event discontinuations and all adverse events, when evaluating individual adverse events as coded by specific preferred terms, did not raise any safety concerns which warranted further action.

In October 2004, the Division again looked at the CV adverse event data contained in the June 7, 2001, study report, focusing on myocardial infarction, angina, and cerebrovascular disorder (since myocardial infarction and stroke were the events of greater concern with rofecoxib) and did not include atrial fibrillation, cardiac failure and pulmonary edema. DNBP felt that no action was needed based on these results, except to further evaluate the events that were subsumed under the term "cerebrovascular disorder."

On October 22, 2004, after assessing the overall adverse event profile for this study, DNBP asked the sponsor to provide clinical narratives for patients who participated in the study and had adverse events that were listed using the WHO preferred term "cerebrovascular disorder." The objective of this request was to clarify whether the patients actually had strokes or transient ischemic attacks.

Based on the narratives provided and reviewed by DNBP, the deaths in the study seem not to be primarily related to thrombotic vascular events (many different presumed causes), and the difference between drug and placebo in the incidence of vascular serious adverse events (or non-serious adverse events in general) does not clearly indict the drug.

Our conclusions that no action was needed was based on the fact that the events were small in number in both treatment groups, not uncommon in older individuals, not strikingly different in incidence between the drug and placebo groups, and in some instances more common, in fact, in the placebo group.

This study did not play role in the Agency's assessment of the heightened CV risk from Vioxx shown by the VIGOR trial as it was an Alzheimer's study and was not designed nor did it focus on those endpoints.

Question 5. You mentioned in the Q&A that drug sales representatives are still using egregious marketing techniques-such as detailing, or shadowing of doctors in their offices, offering expensive gifts and samples and honoraria for prescribing physicians-and that those practices have a large effect on prescribing habits. Can FDA encourage drug companies to use better educational techniques, such as peer-reviewed communication of results, to get the word out about new products? Would it help the FDA promote rational prescribing if the FDA had the authority to limit such marketing for recently approved drugs, whose risk-benefit profiles are still not fully understood? If not, why not? How in your view should the concern about promotion to physicians be addressed?

Answer 5. FDA does not regulate practices such as shadowing of doctors in their offices or offering expensive gifts or honoraria for prescribing physicians, and FDA does not regulate the practice of medicine.

FDA's regulations do require that all promotional materials be submitted to FDA on Form 2253 at the same time as they are used to promote to healthcare professionals or to consumers. In other words, FDA's review of promotional materials is generally intended to occur post hoc. If FDA finds the materials to be inaccurate or unbalanced, FDA may take enforcement actions requesting that sponsors stop using violative materials. In some cases, FDA may request that sponsors run corrective advertisements or issue corrective letters to correct product misimpressions created by false, misleading, or unbalanced materials.

CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) is responsible for regulating prescription drug promotion. DDMAC's mission is to protect the public health by helping to ensure that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

Promotional programs and materials performed and disseminated by companies are subject to the labeling and advertising provisions of the FD&C Act. The FD&C Act and regulations do not distinguish between promotion to professional or consumer audiences. Section 502(n) of the FD&C Act specifies that prescription drug advertisements must contain "a true statement of . . . information in brief summary relating to side effects, contraindications, and effectiveness" of the advertised product. The implementing regulations specify that prescription drug advertisements cannot be false or misleading, cannot omit material facts, and must present a fair balance between effectiveness and risk information.

FDA regulates advertisements and other promotional material, called "promotional labeling," disseminated by or on behalf of the advertised product's manufacturer, packer or distributor. According to the October 2002 GAO report entitled, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, "Promotion to physicians accounted for more than 80 percent of all promotional spending by pharmaceutical companies in 2001." Therefore, the bulk of the Agency's time spent reviewing promotional material, is spent reviewing materials produced for promotion to health care professionals, such as detail aids used by manufacturer representatives, convention displays, file cards, booklets, and videotapes, which is distinct from advertising directed toward consumers.

Thank you again for the opportunity to testify before the committee on this important topic and also for the opportunity to submit these answers for the hearing record. If there are further questions, please let us know.

Sincerely,

PATRICK RONAN,
Assistant Commissioner for Legislation.

RESPONSE TO QUESTIONS OF THE HELP COMMITTEE BY CECIL B. WILSON, M.D.

RESPONSE TO QUESTIONS OF SENATOR ENZI

Question 1. What does FDA do to get important new information about drugs to doctors and patients, short of an actual label change? How might FDA improve their communications?

Answer 1. The primary way by which the FDA communicates information about a drug's risks and benefits to physicians is through the package insert. However, when changing a product's labeling is not appropriate, the FDA relies primarily on electronic means to communicate important new drug or safety information, including the posting of public health advisories directly on the FDA Web site. Approximately 46,000 individuals receive direct e-mail notices of safety alerts that are posted on the MedWatch homepage. Additionally, approximately 160 MedWatch partners, including the AMA, assist in disseminating safety alert information.

The FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it and act on it when prescribing a drug. Potential collaborative activities include:

- Undertaking a major CME initiative on risk communication;
- Working with major medical journals and medical society web site editors to identify standard places for the dissemination of important new risk information about drugs and biological products;
- Using alternative mechanisms to transmit "Dear Doctor" letters, which disseminate important prescribing information from the pharmaceutical companies to physicians (e.g., publication in medical journals, possibly as paid advertisements; placement on medical society web sites; and transmission to individual physicians by blast fax, blast e-mail, or direct daily downloads to personal digital assistants [PDAs]);
- Changing the content and format of "Dear Doctor" letters to emphasize the need for action by the prescribing physician; and
- Encouraging pharmaceutical companies to train and send their sales forces to physicians to educate them on important new risk information about company products.

Additionally, the FDA issued a proposed rule in December 2000 to modify the format and content of the package insert with the goal of making the information more useful and user-friendly to physicians. Their recommendations included a more simplified, "Highlights of Prescribing Information" section within the package insert. The AMA continues to strongly support FDA efforts to make package inserts more useful and user-friendly for physicians and encourages the FDA to issue a final rule to that effect.

Question 2. We have heard that the voluntary and passive nature of the adverse event reporting system may result in under-reporting of safety issues. What can you suggest to this Committee as to how we could improve that reporting? How might new technologies, such as Electronic Medical Records be applied to the Adverse Event Reporting System and what are the benefits one could expect to achieve?

Answer 2. As mentioned in our written testimony, if formal postmarketing studies are not conducted by manufacturers or clinical investigators to obtain safety information, observational data collected by physicians, other health professionals, and patients are the keys to evaluating and characterizing a drug's risk profile in actual clinical use. Currently, the FDA maintains an adverse event reporting system termed MedWatch, which incorporates both a mandatory adverse event reporting system for manufacturers subject to the Agency's postmarketing safety reporting regulations, and a voluntary, adverse event reporting system for health care professionals, consumers, and patients. MedWatch can be an effective tool for detecting signals suggesting that a drug may be associated with a rare, but serious, adverse event.

However, the MedWatch program is a passive system and it is limited by its reliance on voluntary reporting, which inevitably leads to under reporting. Under reporting and uncertainty about the actual extent of drug exposure, make it difficult to estimate true rates of occurrence of drug-induced adverse events. Because of their observational nature, spontaneous reports also are limited in their ability to establish causality. In order to enhance this program, better educational efforts are needed to inform physicians and other health professionals on how, when, and where to report suspected serious adverse events.

Additionally, attention should be directed toward enhancing postmarketing surveillance by using more active approaches. For example, well designed pharmacoepidemiologic studies on newly marketed drugs could substantially enhance our ability to more accurately determine a drug's adverse event profile in a timely manner.

Question 3. I know that there are questions about both quantity and quality of adverse event reports. FDA already receives hundreds of thousands of reports a year, and perhaps should be receiving more. How do they separate the truly important events from the rest? What can treating physicians do to improve the quality of reporting that you do to the FDA?

Answer 3. Based on our understanding, the FDA defines adverse drug events as those occurring: (1) in the course of use of a drug product in professional practice; (2) from drug overdose, whether accidental or intentional; (3) from drug abuse; (4) from drug withdrawal; and (5) from any "failure of expected pharmacological action." According to the FDA, MedWatch is especially interested in receiving: (1) reports of serious adverse event reports that are novel or not currently included in the drug's labeling; (2) all serious events associated with new drugs during their first 3 years on the market; and (3) previously reported reactions if they are serious and occur in clusters.¹

To improve the quality of reporting to MedWatch, better educational efforts are needed to inform physicians and other health professionals on how, when, and where to report suspected serious adverse events.

Question 4. FDA evaluates the risk/benefit ratio of a drug for a population, but doctors and patients evaluate it on an individual basis. Could you comment on the value and limitations of off-label prescribing? Would Federal restrictions on off-label use negatively interfere with the doctor-patient relationship?

Answer 4. Unlabeled (off-label) uses are defined as the use of a drug product for indications or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic Act, a drug approved by the FDA for marketing may be labeled, promoted, and advertised by a manufacturer for only FDA approved uses. Even though the Prescrip-

¹A serious adverse drug reaction is defined as one that results in or prolongs hospitalization, is life-threatening, contributes to significant disability, or results in the death of the patient.

tion Drug User Fee Act (PDUFA) has reduced the review time for Supplemental New Drug Applications or SNDAs, manufacturers are not required to and may not choose to seek FDA approval for all useful indications. This occurs because the expense of regulatory compliance may be greater than the eventual revenues expected. A sponsor may also not seek FDA approval because of difficulties in conducting controlled clinical trials (e.g., for ethical reasons, or due to the inability to recruit patients).

A physician may choose to prescribe a drug for uses, in treatment regimens, or in patient populations that are not part of the FDA-approved labeling. The decision to prescribe a drug for an unlabeled use is made by the physician in light of all information available and in the best interest of the individual patient. Prescribing for an unlabeled use requires the physician to use the same judgment and prudence as exercised in medical practice for it to conform to accepted professional standards. Given the prevalence of unlabeled uses and the fact that in many clinical situations such use may represent the most appropriate treatment (and in some cases the only treatment), the prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care.

The AMA also strongly supports the SNDA process. However, given the disparity between the actual submission of SNDAs and the evolution of evidence-based medical practice, physician prescribing for unlabeled uses should not be impeded by any actions taken to improve drug safety.

Question 5. Could you comment on the value of FDA's new Web site, announced by HHS Secretary Leavitt and Acting Commissioner Crawford, as a step to make sure patients and doctors have the latest and best information about the drugs they are using?

Answer 5. The AMA applauds HHS and FDA efforts to enhance the transparency of the drug surveillance and risk communication processes with the creation of the "Drug Watch" web page. However, the FDA must provide clear advice when it disseminates emerging or preliminary information prior to taking regulatory action.

RESPONSE TO QUESTIONS OF SENATOR HATCH

Question 1. I understood from your remarks that the FDA had over the last several years increased the speed of drug approvals without any decrements in drug safety. The observational data collected by clinicians and patients that is used to evaluate and characterize a drug's risk profile in actual clinical use has received a fair amount of criticism lately. Would you please comment on the limitations and benefits of the current system and any changes you would recommend?

Answer 1. As mentioned in our written testimony, if formal postmarketing studies are not conducted by manufacturers or clinical investigators to obtain safety information, observational data collected by physicians, other health professionals, and patients are the keys to evaluating and characterizing a drug's risk profile in actual clinical use. Currently, the FDA maintains an adverse event reporting system termed MedWatch, which incorporates both a mandatory adverse event reporting system for manufacturers subject to the Agency's postmarketing safety reporting regulations, and a voluntary, adverse event reporting system for health care professionals, consumers, and patients. MedWatch can be an effective tool for detecting signals suggesting that a drug may be associated with a rare, but serious, adverse event.

However, the MedWatch program is a passive system and it is limited by its reliance on voluntary reporting, which inevitably leads to under reporting. Under reporting and uncertainty about the actual extent of drug exposure, make it difficult to estimate true rates of occurrence of drug-induced adverse events. Because of their observational nature, spontaneous reports also are limited in their ability to establish causality. In order to enhance this program, better educational efforts are needed to inform physicians and other health professionals on how, when, and where to report suspected serious adverse events.

Additionally, attention should be directed toward enhancing postmarketing surveillance by using more active approaches. For example, well designed pharmacoepidemiologic studies on newly marketed drugs could substantially enhance our ability to more accurately determine a drug's adverse event profile in a timely manner.

Question 2. How would you recommend we enhance postmarketing surveillance? What more active approaches do you see as promising? How is it best to notify clinicians of changes in practice or new findings? Passive means, such as having them log onto a Web site, are likely to be less effective than more active methods—what specifically do you see as the best practices?

Answer 2. Well designed pharmacoepidemiologic studies on newly marketed drugs could substantially enhance our ability to more accurately determine a drug's adverse event profile in a timely manner.

Furthermore, the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it and act on it when prescribing a drug. Potential collaborative activities include:

- Undertaking a major CME initiative on risk communication;
- Working with major medical journals and medical society web site editors to identify standard places for the dissemination of important new risk information about drugs and biological products;
- Using alternative mechanisms to transmit "Dear Doctor" letters, which disseminate important prescribing information from the pharmaceutical companies to physicians (e.g., publication in medical journals, possibly as paid advertisements; placement on medical society web sites; and transmission to individual physicians by blast fax, blast e-mail, or direct daily downloads to personal digital assistants [PDAs]);
- Changing the content and format of "Dear Doctor" letters to emphasize the need for action by the prescribing physician; and
- Encouraging pharmaceutical companies to train and send their sales forces to physicians to educate them on important new risk information about company products.

Question 3. I appreciate your educating us on the reasons why so many patients are being properly treated by off-label uses of drugs. Do you see the decision by a physician or other clinician to use a drug in this way as an exercise in clinical judgment, in the same way that the physician decides what diagnostic test to use, what diagnosis is the most likely, whether the treatment plan is successful, and so on?

Answer 3. Unlabeled (off-label) uses are defined as the use of a drug product for indications or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic Act, a drug approved by the FDA for marketing may be labeled, promoted, and advertised by a manufacturer for only FDA approved uses. Even though the Prescription Drug User Fee Act (PDUFA) has reduced the review time for Supplemental New Drug Applications or SNDAs, manufacturers are not required to and may not choose to seek FDA approval for all useful indications. This occurs because the expense of regulatory compliance may be greater than the eventual revenues expected. A sponsor may also not seek FDA approval because of difficulties in conducting controlled clinical trials (e.g., for ethical reasons, or due to the inability to recruit patients).

The decision to prescribe a drug for an unlabeled use is made by the physician in light of all information available and in the best interest of the individual patient. Prescribing for an unlabeled use requires the physician to use the same judgment and prudence as exercised in medical practice for it to conform to accepted professional standards. In some instances, prescribing a product off-label is the most appropriate therapy based on the latest, best scientific evidence. In some patient populations, it may be the only treatment option.

Question 4. We have heard several people recommend that the FDA be able to "control" how drugs are used. Do you agree? Should the government, through the FDA, decide how patients should be treated, or is that a matter for the clinician who is caring for that individual patient? Should we instead focus on improving educational outreach programs and surveillance notifications to clinicians?

Answer 4. As stated in our testimony, FDA-approved drug product labeling (i.e., the package insert) should be the primary means by which the FDA communicates risks about drug products to physicians for the vast majority of drugs. Higher level risk communication and risk minimization tools that extend beyond the package insert, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk drug products with truly unique and important benefits on the market.

In the government's efforts to improve drug safety, there may be a desire to use, more routinely, risk minimization tools that extend beyond not only the package insert, but also beyond targeted education and outreach in an effort to improve drug safety. A number of these approaches would directly manage or restrict physician prescribing and may lead to unintended consequences.

Rather than focus on restrictions, the AMA believes that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innova-

tive ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it and act on it when prescribing a drug. The AMA encourages the FDA and the product sponsor to work with relevant physician organizations to assure that the minimum number and least intrusive tools are selected to achieve the risk minimization objective.

The AMA believes that individual States should regulate the practice of medicine. AMA policy provides that, “the AMA and interested physicians will continue to work with the Food and Drug Administration to prevent the unnecessary intrusion of the government and other regulatory bodies into the doctor-patient relationship, especially as it concerns the prescription of medication.” (AMA Policy H-100.971).

RESPONSE TO QUESTIONS OF SENATOR KENNEDY

Question 1. Why do you believe that direct-to-consumer ads that encourage patients already in treatment to ask their doctor about prescribing a particular drug or switching them to a new drug are so effective? Why are drug companies spending so much time and money shadowing doctors, and showering them with gifts and honoraria and samples, as part of their marketing? I assume that all of these practices work in getting physicians to prescribe drugs they wouldn't have otherwise. Is that beneficial?

Answer 1. The AMA supports patients' increased access to drug information, but is concerned about the impact direct-to-consumer (DTC) advertisements have on the physician-patient relationship. In consultation with the FDA, the AMA developed guidelines (AMA Policy H-105.988) in 1993 for acceptable DTC advertisements. These advertisements should promote accurate, balanced information that can provide educational benefit for consumers. The AMA policy also urges the FDA and the pharmaceutical industry to conduct or fund “independent” research to study the effects of the DTC ads on the physician-patient relationship, health outcomes and costs.

Regarding gifts given to physicians by pharmaceutical companies, some gifts that reflect customary practices of the industry, may not be consistent with the AMA Principles of Medical Ethics (AMA Code of Medical Ethics E-8.061). These Principles were developed by the AMA's Council on Ethical and Judicial Affairs and are designed to guide physicians on the inappropriateness of accepting gifts from the pharmaceutical industry.

Question 2. Besides asking for FDA help in getting better quality information to doctors and patients, what is the American Medical Association doing to ensure that doctor's prescribing habits are based on peer-reviewed evidence, rather than on clever marketing to doctors and patients? Are those strategies working? Does the FDA need to step in and regulate communication between the drug industry and the public or the promotional goods and services offered by the drug industry to prescribing doctors?

Answer 2. The AMA supports activities designed to foster the development and implementation of evidence-based, physician-level clinical quality improvement efforts. The AMA convened the Physician Consortium for Performance Improvement to identify and develop performance measurement resources for physicians. The Consortium is comprised of clinical content experts from more than 60 State and medical specialty societies, methodological experts, the Agency for Health Research Quality (AHRQ) and the Center for Medicare and Medicaid Services (CMS).

Through publication of the *Journal of the American Medical Association* (JAMA) and the Archive specialty journals, the AMA is the world's leading medical organization in publishing peer-reviewed articles intended to inform and guide evidence-based clinical practice. Additionally, the AMA is a leader in providing Continuing Medical Education (CME) activities. In 2004, the AMA sponsored more than 320 CME activities serving more than 43,000 physicians.

The AMA believes that individual States should regulate the practice of medicine. AMA policy provides that, “the AMA and interested physicians will continue to work with the Food and Drug Administration to prevent the unnecessary intrusion of the government and other regulatory bodies into the doctor-patient relationship, especially as it concerns the prescription of medication.” (AMA Policy H-100.971).

RESPONSE TO QUESTIONS OF SENATOR ENZI BY KEITH L. CARSON

Question 1. Personalized medicine intrigues me. Each product is a small market but the field overall has huge potential. How do we make the drug development process efficient enough to make these products worth pursuing?

Answer 1. Personalized Medicine will allow doctors and drug companies to identify individuals who are genetically susceptible to certain diseases, as well as those who have a propensity to either respond well to, or experience an adverse event from, certain drugs. With this information, doctors will have a better chance to prescribe drugs to which a patient will respond well, and avoid drugs to which a patient will have problems. The product manufacturers will also be able to use this information in clinical trials to select patients who would probably do well in the trial, and avoid patients who could have adverse reactions.

Genetic mapping could therefore revolutionize medicine by making drugs work better while avoiding undesirable reactions. Clinical trials could be done with smaller patient populations and result in fewer adverse events. The product development cost savings could be tremendous, plus the welfare of the clinical trial participants would be greatly improved.

Personalized Medicine would not necessarily result in small markets for each product, but would improve the performance of products while preventing harmful side-effects. If patients were identified as having a higher probability of bad side effects with a product, no one would want them to take it. The use of this technology could prevent a tremendous amount of litigation costs and settlements that now result from drug related adverse events and deaths.

The potential savings from smaller clinical trial populations and fewer patient lawsuits are such that product developers (biopharmaceutical companies) will eagerly adopt this new technology and use it extensively.

Unfortunately, there are significant problems associated with Personalized Medicine. Many patients will be reluctant to have their genes mapped, since they don't know how the information will be used, or by whom. In addition, very large databases will have to be built and managed to share enough information for Personalized Medicine to be effective. Doctors will have to do a far better job of sharing patient response data, and product developers will have to share what they now consider proprietary clinical data with the public and other companies.

Question 2. What other emerging technologies might be useful in identifying at-risk patients or populations and/or predicting potential adverse events? Are there processes in place for the use of these technologies in regulatory decision-making? What are some of the hurdles to validation, regulatory acceptance and broad application of these technologies?

Answer 2. I'm not aware of technologies other than pharmacogenomics (gene-mapping) that have this potential. However, gene-mapping technology currently relies on the use of microarray technology, plus datamining and *in silico* technology to establish the correlations needed for it to be useful in Personalized Medicine.

I know that the FDA is trying to build up their technical capabilities in this area, so that they can better understand the technology and apply it. However, I'm sure they will need more funding to do this properly.

FDA is the only entity that has access to all of the clinical trial data that is submitted. They are in a unique position to manage this data and make it available for correlations to patient gene-mapping. However, such an endeavor will take massive data storage and computing capability.

I suggest that Congress provide adequate funding so FDA can have outside firms provide the necessary storage and analysis services. Such services are becoming a commodity and prices are very competitive. FDA doesn't have the internal expertise to build and maintain a state-of-the-art capability, and they certainly don't have the hardware. They should rely on outside contractors as much as possible.

Once a large enough database has been assembled, then FDA could use the data to make comparisons between similar products, and help make better regulatory decisions concerning the design and size of clinical trials, plus the selection of specific patients for these trials. As more clinical data became available for a particular product, the Agency could even decide that the product should be licensed for specific patient profiles, while other studies continued.

To validate or accept this technology, sufficient data will be needed. Product response data is required to show which patients did well or had problems with a certain drug. Adverse events will have to be experienced to establish the correlations needed to predict which patients could be susceptible to them. To get this data, product developers must be more willing to share clinical data with the public and other companies, and doctors must do a better job of reporting how patients respond to new drugs.

In addition, patients will have to become more comfortable with having their genes mapped. Many people are concerned about how this information will be used. They are especially fearful of what insurance companies and employers could do

with the data. Systems must be devised that provide adequate data encryption and controlled access.

Question 3. What one action could Congress take that would most dramatically improve drug safety in the U.S.?

Answer 3. Congress could increase funding so that FDA can fully utilize this new technology. In addition, Congress could work with AMA to implement better electronic systems through which doctors can report drug responses—good and bad.

RESPONSE TO QUESTIONS OF SENATOR HATCH BY KEITH L. CARSON

Question 1. Do you believe that the lack of a modern IT infrastructure at the FDA impairs the agency's ability to do its job and hire the best people?

Answer 1. I believe that the lack of modern IT infrastructure will severely impede FDA's ability to utilize new technologies such as advanced data management, datamining, and *in silico* technology. FDA is the only entity that has access to all the clinical trial data that is submitted, and has a unique opportunity to make this data available for use in Personalized Medicine.

To acquire adequate infrastructure, I suggest that much of it should be obtained through services from outside contractors. However, significant upgrades will still be needed for internal data management capabilities that should not be outsourced.

I don't know if a lack of IT infrastructure is keeping FDA from hiring the best people, but it could certainly prevent top-notch IT people from joining the Agency.

However, FDA budget restrictions provide a far bigger impediment to capturing the best people. The Agency is known for having a very tight budget, where everything is difficult to justify and buy. Top technical people will go where the resources are available for them to do the best work.

Question 2. Is the FDA competitive when it comes to attracting new staff? What do you believe that the FDA should do to attract the best and brightest scientists?

Answer 2. I seriously doubt that FDA is competitive when it comes to attracting new staff. FDA is constantly losing good people to industry positions that pay far more money and provide vastly superior resources. In addition, these industry positions don't involve the political and bureaucratic hassles that an Agency job is known for. At FDA, every decision must be scrutinized as to ethical and legal implications, plus pass through multiple levels of management. Such an environment stifles innovation and sound decision making.

To attract the best and brightest scientists, FDA must have the resources to equip, supply, and staff their laboratories. Without proper funding, good people would never put up with the bureaucratic hassles and red tape that the Agency is known for.

The FDA does have some very talented and brilliant people, who are truly dedicated public servants. I could not work under the pressures, internal politics, and bureaucratic nightmares these folks endure on a daily basis. Then, when their programs are drastically underfunded, I don't know how they can take it. We should all be proud to have the folks that are there, and Congress should do all it can to adequately fund FDA's laboratories.

RESPONSE TO QUESTIONS OF THE HELP COMMITTEE BY RAYMOND L. WOOSLEY, MD, PH.D.

RESPONSE TO QUESTIONS OF SENATOR ENZI

Question 1. In your testimony, you describe some initiatives for tracking outcomes of treatment with new drugs, particularly the UK's "yellow card" system. The UK has a national health care system, unlike the US. How do you envision setting up a physician-based national drug safety evaluation system in the absence of a national health care system?

Answer 1. I don't think such a system is the best approach for the United States. The cost of reimbursing physicians would make it too expensive to implement and it would compete with physician's time to allocate for patient care. That is why I have suggested a pharmacy-based system for drug safety. The expertise of pharmacy technicians, pharmacists and clinical pharmacists are under-utilized and would cost far less than a physician-driven system. The proposal described in my written testimony would be community-based and focused on outpatient healthcare. We would also need to have a hospital-based pharmacy network. The principles would be the same.

We would give pharmacy technicians, pharmacists and clinical pharmacists special training in drug safety surveillance using a curriculum designed by the AHRQ-funded Centers for Education and Research on Therapeutics (CERTs). They could receive the training through distance learning (such as “telemedicine”). The surveys (questionnaires developed by the FDA and CERTs collaborators) would be performed by pharmacy technicians. Specially trained pharmacists (for outpatients) and clinical hospital pharmacists (for inpatients) could address the interpretation of medical information and contact physicians when necessary to obtain more detailed information.

The Quality Improvement Organizations (QIOs) funded by the Centers for Medicare and Medicaid (CMS) could assist by abstracting medical records, a function they now do under contract for CMS. The information gained would not only improve outcomes (which both increases safety and lowers cost to CMS), it would provide data for the FDA Office of Drug Safety that is not now available.

The data would also be rapidly available so that the number of people exposed to risks should be minimized. For the 15 drugs removed from the market since 1997, it took an average of 5.9 years before the harm was detected and final action taken. I envision a rapid response system that saves lives and therefore limits liability for companies in subsequent litigation.

Question 2. I am intrigued by your suggestion of a staged approval process for new drugs. However, I’m concerned that there would be great demand for a new drug as soon as it is approved. Patients who are desperately ill want and need access to new treatments. Could you tell me more about how you would restrict access to these drugs?

Answer 2. I hesitate to use the word “restrict” because I share your concern for patients who need new medicines. I think we need a process that makes the drug available as early as possible but only for those patients who are representative of those for whom a new drug has shown benefit. If a drug has only been tested in patients with a certain type of cancer and patients with renal or liver disease have never been studied, we should prohibit or at least strongly discourage patients with renal disease from receiving the drug. Likewise, the very elderly should be discouraged from taking a new drug if it has only been studied in younger people. Perhaps, they could only get the drug under a registry system so that we would know what happens when the drug is used off label.

Every drug will be different and we need a system that is flexible enough to rapidly respond to patient needs. Once in place throughout the country, the Community Based Pharmacy Safety Network described above could perform this type of function.

While some may argue this system would limit the ability of doctors to prescribe approved drugs for any use they deem appropriate, I suggest it would provide a proper balance between the rights of medical practitioners and the rights of patients to receive safe and effective drugs for their particular medical issues.

Question 3. What one action could Congress take that would most dramatically improve drug safety in the U.S.?

Answer 3. I agree with Acting Commissioner Lester Crawford in his recent testimony that (and I paraphrase) the best way to address drug safety is to enable the FDA to pursue the Critical Path Initiative described in the white paper: “Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products.” I recommend that Congress provide the FDA with \$50 million in funding for the Critical Path Initiative to utilize the currently available mechanisms to both enhance drug safety and enable the development and approval of new drugs for serious medical conditions.

The drug safety problem cannot be solved by the FDA alone. These funds would enable the FDA to work with its sister agencies (CMS, AHRQ, CDC and NIH), the academic community and the industry to address drug safety and the interrelated problems that result from the lack of innovation in the process of drug development.

RESPONSE TO QUESTIONS OF SENATOR HATCH

Question 1a. You mention that the pharmaceutical industry spends 12–15 years and nearly a billion dollars on each drug that is successfully developed. You also describe that the proportion of drugs that fail during development has doubled in the last 10 years. Why is that?

Answer 1a. The most complete answers to this question can be found in the FDA’s white paper that was released in March of 2004: “Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products.” First, I should expand on my testimony: Estimates range from \$850 million to \$1.7 Billion

for the amount that the industry must spend overall in order to get one drug approved. This includes the cost of many drug failures. The amount spent on any one drug that succeeds is actually less, probably about \$400 million. However, the cost of failures is a real cost and one that must be accounted for. The rising number of drug failures, both before and after marketing, adds tremendously to the cost of pharmaceutical research and development. Since 1997, 17 major drug products were removed from the market. The costs of their development were in the billions of dollars and should be considered a loss from the standpoint of "opportunity costs." Removing these drugs from the market also is associated with billions of dollars in losses due to litigation and personal injury claims.

A short answer to your question is the following: Over the last twenty years we have had a revolution in science that has created new opportunities to learn more about the medicines that are being developed. The FDA has required that drug companies add research projects to the development process in order to know more about the drugs and how to use them. For example, the FDA now asks companies to identify which enzymes break down the drug because we know that some people, due to their individual genetics, can fail to break down the drug, which could build up in their bodies to cause harm.

We now know that two drugs can interact when taken together, so we ask companies to do specific studies to test for drug interactions before marketing. We now know that some drugs from every possible class can have effects on the heart that result in potentially lethal heart rhythm abnormalities. We now ask companies to conduct studies to screen for this problem.

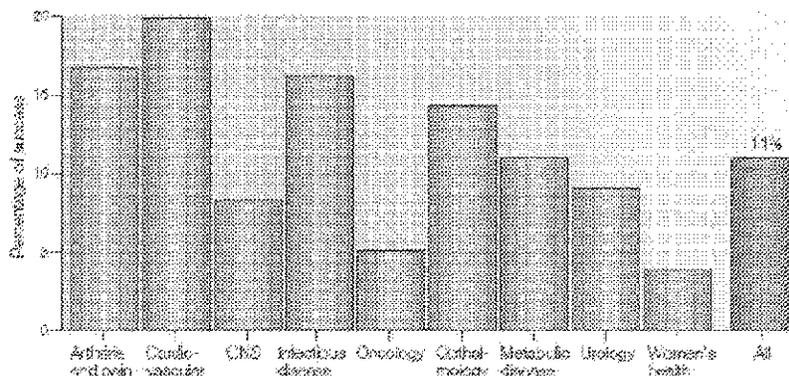
These are but a few of the many important new requirements that have improved our understanding of how to use medicines more safely. However, these requirements add time and expense to the development process. On the other hand, there are opportunities to remove certain requirements from the traditional process. For example, we still require that all companies conduct studies to determine in two rodent species (usually rats and mice) the dose of the new drug that kills half of the animals. Often rodents don't have the same proteins as humans so the studies may never be relevant. However, there is no ongoing process for the FDA to meet with other scientists in drug development and reach a consensus on what work should no longer be required.

It will take a very special process that brings the very best science and a willingness of all involved to share data and experience. That does not now exist, but it is the kind of partnership called for in the Critical Path Initiative ("Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products").

Question 1b. Do you know how many drugs are not brought to market? In other words, how much money and time does the pharmaceutical industry invest in research that does not result in a new marketable drug?

Answer 1b. Estimates are that only 11 percent of drugs that enter clinical testing are ever approved. Therefore, for every drug approved, nine others fail. Since only about 30 new drugs are approved each year, approximately 270 fail using these numbers for projection. The figure below is taken from *Nature Reviews: Drug Discovery*, 3 (8): 711, 2004. It shows the percentage of successful drugs in each class.

It is difficult to know how much the industry loses on drugs that fail but it could be as high as 55 percent of their \$40 billion annual investment in research and development. I base this on current estimates that a company must plan to spend about \$400 million on a successful drug and the fact that \$875 million is the final cost per drug including failures. Unfortunately our ability to predict failure is getting worse, not better. Again the work proposed in the Critical Path Initiative would help by developing "biomarkers" for many indications that could more accurately predict the safety and effectiveness of drugs.



Question 2. You testified that industry investment has increased by 250 percent over the last 10 years, but the number of new products submitted for FDA review has fallen by 50 percent. Why is that?

Answer 2. I believe the rising cost and protracted development times have deterred companies from taking more new drugs into development. The consolidation of the pharmaceutical industry has also been a major factor. Since 1980, 48 companies have collapsed into six and with every merger or purchase a large number of drugs have been taken out of development. Also, since 1995, the number of failures during development has risen and only half as many drugs now succeed to reach market.

Question 3a. You mention that over half of the 15 drugs that were removed from the market for safety concerns over the last 8 years were in fact safe when used as directed. Should these drugs not have been removed?

Answer 3a. If we had an effective means to assure their safe use (i.e., in which use is limited to those conditions where safety and efficacy have been proven), these drugs could have remained on the market. This is why the FDA must partner with CMS and AHRQ and others to find ways to better inform healthcare providers in ways that result in safe medication use. The Centers for Education and Research on Therapeutics (CERTs) were authorized by Congress with this task. However, the CERTs have been too small in number and inadequately funded to accomplish this task. Also the FDA has not had sufficient staff or resources to work on this with AHRQ and the CERTs. CMS and other insurers are the financial benefactors if this can be accomplished.

When terfenadine was removed from the market, the generic form of the drug had just been approved by the FDA. However, when it was removed, it left only the very expensive brand named non-sedating antihistamines. Billions of dollars spent on these antihistamines (Claritin, Allegra and Zyrtec) could have been saved if generic terfenadine could have remained on the market and used safely, i.e. in a way in which it was not taken with drugs such as erythromycin that interacted and made its use dangerous.

Question 3b. If they were effective when used according to their indications, did not their removal harm those patients who had been using them properly and receiving benefit from them?

Answer 3b. Indeed. For some of these drugs, there was no alternative therapy and patients and doctors lost the benefit of effective therapy. For some, there were alternatives but, as mentioned above for terfenadine, the alternatives were very expensive and caused financial hardship for patients. Vioxx is another example where it was intended for patients at risk for gastrointestinal bleeding. Now, they do not have access to this safer drug and may be harmed by the available agents. By removing Vioxx from the market, the underlying issues of why Vioxx and other Cox 2 inhibitors were developed and approved have not gone away.

Question 4. Is the problem in drug development the lengthy, extensive, and yet inadequate approval process which costs so much, or is it the limited time the company is allowed to recoup its R&D costs before generic competition? Or is it the liti-

gious environment in which we live that leads to the industry's heightened fears about labeling or lawsuits?

Answer 4. These are all contributors to the problem. However, I would not favor extending the patent coverage. This would only encourage and reward further inefficiency. We should focus on improving (i.e., shortening) the process. AIDS drugs were developed in an average of 3 years without risk to patients. That should be the model for all drugs.

Question 5a. You mention that "once a drug is marketed, the FDA has no control over the way it is used in clinical practice." Should the FDA control this?

Answer 5a. No, I do not think the FDA should control the practice of medicine. This should be controlled by professional societies. However, we must encourage better prescribing in every way possible. One way that is being addressed by Dr. Mark McClellan, the head of CMS, which involves the way we reimburse caregivers. He believes that payors like CMS should reward evidenced-based practices. We do not do that today. We pay the same for a visit in which a drug was prescribed inappropriately as we do for a visit in which the drug was prescribed in ways proven to be safe and effective. By rewarding evidenced-based practices, CMS can help FDA be sure the drugs they approve are used safely.

Question 5b. Or should clinicians? Isn't there a partnership between the FDA and practitioners?

Answer 5b. I don't think there is such a partnership. The FDA writes labels for drugs that do not result in safe practice. The FDA has to resort to removing drugs from the market because its "Dear Doctor" letters are too often ignored, both by doctors and by pharmacists.

Question 5c. Isn't it the role of continuing medical education—and in a worst case scenario our malpractice system—to ensure that practitioners are using drugs appropriately?

Answer 5c. Research has shown that conventional continuing medical education (CME) programs do not effectively improve the practice of medicine. CME when provided by pharmaceutical companies yields increased use of a medicine but that is not always the best practice of medicine. Vioxx is again a great example, where it was promoted through CME programs that resulted in its overuse, i.e., use in patients without risk of gastrointestinal bleeding.

Yes, physicians fear malpractice claims and that fear affects the way they practice medicine but not always in ways that we would prefer. For example, physicians order unnecessary lab tests to guard against claims that are unlikely to occur. They often prescribe unnecessary medicines because they are afraid they will be accused of doing nothing to help the patient. Healthcare providers want to prescribe the very best medicines for their patients. When they fail to do so, it is often the "system" that has failed them. For example, many times drug interactions occur because the physician is unaware of medicines prescribed by other doctors.

Question 6a. If the FDA receives the authority to demand further research on marketed drugs, does this also imply they will have the responsibility to fund the research as well?

Answer 6a. I would not recommend giving the FDA the authority to require companies to do research after a drug is marketed. Instead, I suggest that the FDA, NIH and AHRQ work with the drug company sponsor to agree upon what research is needed. The FDA and NIH or AHRQ should conduct the agreed upon studies with funding from user fees paid by the sponsor. Since the studies would be conducted by NIH and/or AHRQ, there would be less concern about the validity of the research. While such research is being conducted, the FDA should be given the authority to change the way the drug is marketed and distributed. It should be allowed to suspend direct to consumer advertising. It could work with AHRQ and insurers to prohibit payment for off label prescription if the use is possibly dangerous or of unproven value. For example, if a drug is considered potentially unsafe for very elderly patients and safety studies have not been conducted in this population, CMS and other insurers should not provide payment for the drug in those patients. If these limitations are inadequate to protect the public, the FDA should also be given the authority to suspend marketing. During this suspension, every effort should be made to make the drug available to those for whom there are no alternative therapies of serious illnesses.

Question 6b. If they are not going to fund it, will the companies? And what will happen to those patients who are benefiting from the drug if the company decides

that it is more cost effective to remove the drug from the market rather than do additional studies?

Answer 6b. The drug companies will resist changes in post marketing research and surveillance because they will want to retain control over the research on their products. It is unlikely that they would conduct research projects unless they agree upon the methods to be used. It will be difficult for NIH or AHRQ to conduct research on drugs unless the manufacturer is not in agreement. The company will have to provide the medications for the study and they often control the manufacturing process. Therefore, I think it is important that this research be mutually agreed upon. The FDA will need leverage in order to see that the research is done in the best way to protect the public. For this reason, the FDA must have the authority to suspend direct to consumer ads, suspend sales, etc.

Compared to the potential profits from a marketed drug, the cost of most studies is only a small fraction. I do not think a company will choose to remove a drug from the market because of the need for more studies. The incentive of having a larger market or less legal liability should encourage a company to collaborate in the necessary research.

Question 7. How should we replace the “user fee” system so as to avoid linking industry support to the FDA’s work and performance while simultaneously ensuring that the FDA has the funds it needs to carry out its mission?

Answer 7. The funds that are needed to support the FDA should be provided by all companies and based on a fraction of sales. The funds should pay for all of the activities of the FDA, not just review of new drugs and/or devices. I recognize that these charges could lead to higher prices for consumers (although market forces can limit pricing, especially in a world where more efficient and faster safe drug development is practiced). However, even if some prices are higher, patients and the public health will be better served by having the FDA adequately funded to perform its mission.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY

Question 1. Could you please elaborate on why the post approval drug safety surveillance system needs to be enhanced? Please describe the components of a robust system for post approval safety monitoring, including your community pharmacy safety net project?

Answer 1. Although some tout the current safety system for its ability to detect rare adverse events, it is dangerously inefficient and slow to respond. The 15 drugs removed from the market over the last seven years were on the market for an average of 5.9 years before they were detected by the spontaneous reporting system and removed from the market. One of the major limitations of the current system is the lack of ability to detect rare events quickly and to estimate the frequency. Another weakness is the inability to conduct comparative safety analyses.

Therefore, the ideal system would have the following characteristics:

1. Ability to detect rare adverse events very early after marketing.
2. Ability to accurately quantify the incidence of rare adverse events.
3. Ability to compare the safety of alternative therapies.
4. Ability to detect adverse events that are restricted to special populations, e.g., children, the very elderly, patients with renal or liver disease, etc.
5. Ability to detect adverse events under special conditions of use, e.g., nursing homes, hospitals, hospices, etc.
6. Ability to identify risk factors associated with the adverse event, e.g., presence of other illnesses, biological sex, concomitant medicines, etc. (This information will be essential in the design of methods to prevent or minimize future occurrences of the adverse event.)
7. Ability to focus on potential adverse events identified by FDA medical reviewers during review of a new drug application.
8. Ability to address specific questions that arise after the drug is on the market.

The community pharmacy safety net would address many but not all of these requirements. The following is a plan that The C-Path Institute is developing for a pilot project to be conducted in community pharmacies:

The Community Pharmacy Safety Network (CPSN)

A Community-Based National Medications Safety Program

The most effective means of maximizing the benefit and minimizing the risk of harm from medicines is to have every member of the healthcare team, including patients and their families, fully informed in how to use medicines safely. The

current healthcare delivery system fails to adequately inform patients how to use medications optimally and fails to provide the U.S. Food and Drug Administration (FDA) with adequate information about the outcomes of medication usage. This is a proposal for the creation of a novel community-based network of individuals trained to help patients maximize the benefits of their medications and also trained to obtain reliable data for the FDA on the beneficial and adverse outcomes of medicines. This is information not currently available in any database.

A pilot demonstration program for the nation will be conducted in Southern Arizona by the CPSN. The Critical Path Institute and the Arizona Center for Education and Research on Therapeutics (AzCERT) will develop two special curricula for certificate programs in the Pharmacy Technician training program at Pima Community College and the College of Pharmacy at the UA. This curriculum will enable Certified Pharmacy Technicians (CPTs) and certified pharmacists to aid patients in the safe use of new medications and medications in general. CPTs will also maintain a log of patients receiving pre-specified medicines and obtain baseline and follow-up information from those patients to determine the outcome of their therapies. Scientists in the Arizona CERT will participate in the development of the curriculum and the evaluation of the effectiveness of the program. Scientists from CERT, C-Path and the FDA will collaborate to identify medicines to be monitored, define comparator cohorts and prepare survey questions to define outcome parameters for each cohort of patients. The CPTs will enter the survey results into a web-based database for analysis by the Office of Drug Safety at the FDA. When complex medical events are detected by the CPT survey, a Certified Pharmacist with special training in drug safety will gather information and submit a report to the FDA using standardized MedDRA terminology. The Pharmacist will also report to the prescribing physicians informing them how their patients responded to their therapies and provide summary information from the FDA so they can benchmark their practice to the experience of other physicians and patient populations.

The CERT will evaluate the impact of the CPSN on patient safety by comparing the outcomes of patients who were given special training in the safe use of their medicines by CPTs to the outcomes in a matched control group receiving routine conventional care. If this pilot is successful, the overall cost of medical therapies should be reduced justifying future payment by insurers for CPSN services.

When operational, this system will be able to conduct prospective post-marketing surveillance for drugs. Unlike current systems, it will be able to determine the denominator (number exposed) for adverse events and, when comparator drugs are available, comparative safety of drugs will be determined. The CPSN will be able to determine how drugs are being prescribed and if there is evidence of their effectiveness in new diseases or uses. Because CPSN will provide greater assurance that drug safety will be effectively monitored and adverse events detected earlier, it will be possible for the FDA to accelerate the approval of new drugs without compromising the public safety. The CPSN will also enable patients to play an active role in the management of their therapies reducing the risk of preventable adverse events and hastening the detection of unanticipated adverse reactions.

Question 2. Please describe how our responses to bioterrorism and to drug safety might overlap and complement one another?

Answer 2. Because of the almost unlimited number of biologicals that can be used in bioterrorism, it will be necessary to have the capacity to develop a broad range of preventative or therapeutic drugs quickly. It is unlikely that there will be adequate time to test the drugs completely, so it will be essential that we have a work force prepared and trained in drug safety analysis and surveillance to participate in the evaluation of any new agents employed in the response to bioterrorist attacks. The Community Based Pharmacy Network and other needed programs can be essential elements in a plan for being prepared for safety surveillance. The same curriculum used to certify pharmacists and pharmacy technicians can be used to train members of the military to conduct safety assessment of any new drugs being developed for bioterrorism.

RESPONSE TO QUESTIONS OF SENATOR ENZI FROM BRUCE M. PSATY, M.D.

Question 1. You support creating an independent Office of Drug Safety. This could result in an office that only looks at problems. Isn't it more appropriate for risks and benefits to be considered together?

Answer 1. It is appropriate, even essential, for the new independent Center for Marketed-Drug Evaluation and Research (CMDER) to consider both risks and benefits. The FDA needs to be reorganized to achieve this new division of labor: (1) the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) reviews New Drug Applications (NDAs) or supplemental NDAs (sNDAs) and assesses the risks and benefits of drugs before approval; and (2) the new CMDER reviews and assesses the risks and benefits of prescription drugs after approval. Consultation and coordination between CDER and CMDER around the time of drug approval will be important. At the time of approval, authority to regulate the new drug will pass from CDER to CMDER. Reorganization of the FDA to achieve this new division of labor—pre-marketing evaluations by CDER and post-marketing evaluations by CMDER—will eliminate the conflict of interest that OND currently has in evaluating the post-marketing safety of drugs that OND had approved in the first place.

CDER's OND is effective at reviewing and approving new drugs, and many of the FDA reviewers there are skilled in conducting the pre-approval reviews. But when drugs go on the market, they are used by large numbers of people, many of whom would not have been eligible for the pre-approval trials. What the American public needs and deserves, in addition to the rapid approval of drugs, is a new FDA CMDER whose primary mission, vision and values are geared toward monitoring and assessing the safety and efficacy of drugs that are on the market. Post-marketing surveillance is a different mission, and needs to be a separate but equal partner with CDER's pre-approval evaluation. The new CMDER will need the skills of public health scientists, epidemiologists and ethicists to evaluate the risks and benefits to the population as a whole. Provided with new authorities, the independent CMDER can pursue aggressively key safety questions that industry would sometimes prefer to ignore and protect the health of the public by considering not only the risks but also the benefits in the populations that actually use the new drugs. Regular congressional oversight can help to assure the quality of FDA efforts at both CDER and CMDER and provide an important forum for the discussion of drug efficacy and safety.

Question 2. You have indicated that the Office of Drug Safety is underfunded. Could you comment on the adequacy of the President's proposed fiscal year 2006 budget for FDA, which includes a 24 percent increase for FDA's post-market safety program? If this figure is not adequate, how much funding would it take?

Answer 2. The proposed increase of \$6.5 dollars (24 percent increase) for the FDA's post-marketing safety program in fiscal year 2006 is not adequate. The first 10 years of PDUFA, between 1992 and 2002, did not permit user fees to be used for drug safety activities. According to the General Accounting Office report on the effects of user fees:¹ "The implementation of PUDFA has been successful in bringing new drugs and biologics to the U.S. market more rapidly than before. However, maintaining adequate funding for approving new drugs and biologics has had the unintended effect of reducing the share of funding and staffing for other activities" including drug-safety-related activities. "According to FDA officials," the GAO report continues,¹ "safety problems not detected in clinical trials are more likely to be found first among U.S. patients because they are increasingly first to have access to new drugs." In 1992, when America began to serve as a major drug-safety testing ground, there was little or no attention to enhancing drug safety efforts. According to Dr David Kessler,² former head of the FDA, "PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that We wanted it. The industry said no." The development of infra-structure, described in response to Senator Hatch's first question, remains a major unmet need and will require considerable investment.

In the preparation of the March 2003 report, "FDA's Review Process for New Drug Applications,"³ the Office of the Inspector General conducted a survey of 401 CDER reviewers. Fully "66 percent of FDA respondents indicated on our survey that they were somewhat or not at all confident that the FDA adequately monitors the safety of prescription drugs once they are on the market."³ The lack of trust and confidence in the FDA post-marketing surveillance system, expressed by FDA reviewers, is shared by many independent scientists. The FDA's meager post-marketing surveillance system is further stressed by the mounting challenges. In the 8-year period between 1995 and 2003, the number of post-marketing adverse event

reports received by the FDA MedWatch adverse-event reporting system increased by 137 percent, from 156,477 in 1995 to 370,887 in 2003.^{4,5} In the 4 year period between 1997 and 2001, retail spending on prescription drugs almost doubled, increasing from \$78.9 billion in 1997 to \$154.5 billion in 2001.⁶ Over the same time period, the 50 percent increase in the FTE at the Office of Drug Safety lagged far behind the huge increase in the exposure of the U.S. population to prescription drugs.

The current needs of the new Center for Marketed Drug Evaluation and Research represent not just “current needs” but also an array of previously unmet needs, some of which have accumulated for more than a decade. A serious effort to improve drug safety in America will require a substantial investment. Infrastructure and collaborations for safety studies that have been ignored for a decade need to be developed. In order to protect the health of the public, the budget for the new CMDER will need to move, over the next several years, close to the level of the budget for the OND. Required funding levels will depend in part on the existence of new authorities. If the CMDER cannot compel the pharmaceutical industry to conduct key post-marketing studies and if CMDER has to fund the conduct of independent studies, the funding requirements for drug safety would be especially large.

Question 3. You support a mandatory Federal registry of clinical trials. How would you set up a results database so that the information is actually useful for patients and providers?

Answer 3. The International Committee of Medical Journal Editors has called for clinical trial registration and for “full transparency with respect to the performance and reporting of clinical trials.”⁷ The rationale is important. To use drugs wisely, patients and physicians need to know about risks and benefits. Risk-benefit analyses need complete and accurate information about all relevant studies. The primary purpose of a Federal clinical trials registry is to assure that all randomized trials are fully reported. In the absence of a mandatory registry of clinical trials, the pharmaceutical industry occasionally finds it difficult to resist the marketing instinct to conceal studies with unfavorable findings. In a study of Alzheimer’s patients, for instance, Pfizer’s Celebrex (celecoxib) increased the risk of cardiovascular events.⁸ Although the study was completed in 1999, its results were not submitted to the FDA until June 2001, several months after a safety review that established new labeling for Celebrex. The findings, which were never published, were finally posted on an industry website in January 2005.⁸ This selective-non-publication approach creates a distorted knowledge base so that risk-benefit analyses of Celebrex cannot take into account the cardiovascular harm detected in this study.

For these reasons, the results database of the Federal clinical trials registry will be most useful to scientists who want to conduct reviews and meta-analyses of all the existing studies of a particular drug. The available data and the data structures must be adequate for and useful to these scientists. To make each entry in the database useful for patients and providers, the trial results should include a clear statement of the original hypotheses, its study population, the primary findings in quantitative terms, secondary analyses and safety analyses. The findings from one trial, however, are not adequate to make informed treatment decisions. Instead, treatment decisions should be based on the totality of the evidence about a drug’s safety and efficacy. In other words, patients and providers would do well to seek out independent reviews and meta-analyses of the studies conducted on the drug of interest. Journals often make some of these major high-quality reviews available on their websites without cost to non subscribers. In December 2004, moreover, Consumer’s Union launched “Consumer’s Reports Best Buy Drugs,” which is “a major new public education program that is designed to provide unbiased information about the comparative effectiveness and cost-effectiveness of prescription drugs.”⁹ This service is “provided free to consumers.” The effort to integrate information on the safety and efficacy of new drugs in an independent and unbiased fashion is also an important role for the new CMDER. It is these integrated independent reviews, and not individual entries in the clinical-trials database, that will be most useful to providers and patients.

Question 4. It seems to me that achieving the right balance between the benefit and risk is the key challenge both of approving a new drug and of deciding whether to keep it on the market. What would you suggest could (or should) be done differently so that benefit-risk decision can be made in the best possible way?

Answer 4. The best possible way to make risk-benefit decisions is to have available good scientific evidence from randomized clinical trials that assess the risks and benefits with equal scientific rigor. The pharmaceutical industry expends enormous energy in the effort to demonstrate a drug’s efficacy. For the purpose of evaluating efficacy, industry studies are generally well designed and adequately powered.

But the industry efforts to identify and quantify risks of a drug are modest or less. To an independent scientist, for instance, the known biologic effects of the COX-2 inhibitors would suggest two different hypotheses—the possibility of benefit to the stomach and the possibility of injury to the heart. While many Vioxx (rofecoxib) studies were well designed to assess the potential benefits of pain relief or protection of the stomach, these same studies often minimized the chances of finding any cardiovascular harm. In general, they were small, lasted a few weeks or months, excluded patients with heart disease or patients who used aspirin, and paid little specific attention to cardiovascular events. The evidence provided by this efficacy-driven marketing-focused approach to science—well-studied benefits and ill-defined risks—undermines the validity of a genuine risk-benefit analysis.

The FDA has two major opportunities to help industry address these deficiencies. In the pre-approval stage, the OND can insist that clinical trials examine adequately risks as well as benefits. In addition to the traditional collection of adverse event reports, specific safety outcomes can be defined in advance and assessed in a standardized fashion. Large long-term trials of chronic-disease medicines should be started as early as possible in the drug-approval process. The OND can also insist that patients included in the pre-approval studies are representative of those who will actually use the new drugs. In the post-marketing setting, the new CMDER can address the key questions that remained unanswered at the time of approval. Although 6-week studies may be adequate to demonstrate that drugs such as Vioxx reduce the pain of arthritis in the knee or hip, pain medicines do not cure osteoarthritis, and large numbers of patients with arthritis will take these drugs for many years. Osteoarthritis is common in older adults, many of whom have cardiovascular disease and take aspirin. Under these circumstances, for instance, CMDER can insist on the conduct of post-marketing studies or clinical trials that evaluate the new drug in the patients who actually take them and in the way that these patients actually take the new drugs. In the post-marketing setting, CMDER needs at once to assure that the evaluations of marketed drugs match the way that the marketed drug is used in the U.S. population and, at the same time, to work with physicians and patients to limit the use of the marketed drug to the approved indications and populations. In short, the FDA needs to take a pro-active role in assuring the quantity and quality of the data for risk-benefit analyses, both before and after approval.

RESPONSE TO QUESTIONS OF SENATOR HATCH BY BRUCE M. PSATY, M.D.

Question 1. Do you think that the current post-marketing evaluations are adequate? Could you suggest some specific ways in which they should be improved?

Answer 1. The current MedWatch program is adequate for only one minor, though important, drug-safety effort.¹⁰ This voluntary reporting system is suitable to identify rare serious adverse drug events that occur early in treatment and that are unrelated to the indication of the drug. For example, the lipid-lowering statin drug, Baycol (cerivastatin), was withdrawn from the market in 2001 because it was associated with high rates of rhabdomyolysis, a breakdown of muscle cells that causes pain, kidney failure and sometimes death.^{11 12 13} It would not have been possible to use the MedWatch system to detect reliably, for instance, the increased risk of cardiovascular events associated with the COX-2 inhibitors.

The MedWatch adverse drug-reaction data—recently characterized as “fundamentally a 1950s-era approach”¹⁴ lack many of the features of high-quality epidemiologic studies, including validation of events by standard criteria, complete ascertainment of cases, population-based controls, comparable assessment of drug use and risk factors, and so forth. In short, the current post-marketing surveillance systems are not adequate to meet the new surveillance challenges posed by the rapid approval of new drugs. Several opportunities deserve to be cultivated. First, data from new Medicare drug benefit can be linked with hospital and ambulatory care data to create a new resource for the study of drugs in older adults. With appropriate protections for privacy, these data should be available to the FDA and independent scientists interested in drug safety. Secondly, as part of the NIH Roadmap Project, the HMO-Research Network—Coordinated Clinical Studies Network will create an infrastructure for conducting studies on substantial numbers of the U.S. population, and the movement toward an EPICcare based electronic record among the network members should soon provide the opportunity to conduct post-marketing surveillance rapidly and efficiently.

The development of these “research resources” needs to be complemented by a new public-health vision and sense of mission at the FDA. As indicated in the response to Senator Enzi’s questions, pharmaceutical companies sometimes lack en-

thusiasm for pursuing questions about the safety of their drugs. Although the risk-benefit analysis may appear favorable in the well persons typically recruited to the pre-approval trials, the populations who take new drugs include many groups such as the elderly and those with other serious health conditions. As a result, the risk-benefit assessments may differ markedly in the post-marketing setting from those of the pre-approval-trials setting.

At time of approval, the new independent CMDER should review the NDA and all available data, published and unpublished, to identify the set of studies required to address the key unanswered questions, particularly the pursuit of potential safety “signals” or “plausible biologic hypotheses” on behalf of the health of the public. The current FDA risk-management approach places on the manufacturer the responsibility for defining the safety questions of interest and designing the studies to answer those questions. Rather than serve as simply a reviewer of industry’s proposals, the FDA’s CMDER should actively select the questions, the studies, and the designs that merit attention. CMDER’s work in this regard should be peer-reviewed by independent scientists to assure that the key questions are properly identified and that the studies required to address them are properly designed. Depending on the drug, the indication and the known safety profile, the studies may include Phase IV trials, epidemiologic studies, pharmacokinetic-pharmacodynamic studies, close surveillance of ADR reports, or a combination of several approaches. Specific post-marketing trials or studies should be designed, conducted and completed in a timely fashion. Provisional approval may be another useful approach. The CMDER should be responsible for assessing the balance of risk and benefit of drugs that are on the market.

Question 2. In your testimony, you state that since 1992 funding for drug safety has dwindled. Yet in her testimony, Dr. Sandra Kweder of FDA stated that resources devoted to drug safety, both human and financial, have steadily increased over the past decade. For instance, the ODS budget increased from around \$7 million in fiscal year 1996 to a proposal of more than \$33 million in fiscal year 2006. Likewise, ODS employment has increased during that time from 52 FTEs in fiscal year 1996 to 137 FTEs in fiscal year 2006. Moreover, PDUFA III authorized FDA to use some of its user fee money for risk management activities, and PDUFA resources will represent nearly one third of the ODS budget for the coming fiscal year. Doesn’t this increased funding—both from PDUFA and otherwise—evidence a strong and continuing commitment to drug safety?

Answer 2. As I have indicated in responses to the questions from Senator Enzi, the efforts since 1992 to increase the speed of approval for new drugs have not been accompanied by commensurate improvements on the drug safety side. According to the General Accounting Office report, “FDA reduced staffing levels for non-PDUFA activities each year, leaving the agency fewer resources to perform its other responsibilities,” including safety-related activities.¹ The old system not only produced a “drug lag” that kept new medicines from U.S. patients, but it also provided a “safety buffer” that protected U.S. patients. New drugs would first come to market in Europe; safety problems would be identified there; and the problematic drugs—practolol and thalidomide are examples—would never come to market in the U.S. . Now, with America as the new drug-safety testing ground, the “safety buffer” has been replaced by a “safety lag.” Today, U.S. patients remain at risk of large-scale injuries such as the tens of thousands of heart attacks and strokes caused by Vioxx. The U.S. drug safety systems were not originally upgraded to meet the new challenges of PDUFA in 1992; infra-structure and collaborations have not been developed to conduct new studies rapidly or efficiently; and in recent years, the spending on prescription drugs and the reporting of adverse events have expanded much faster than the resources provided to ODS. The budget increases thus remain inadequate.

Question 3. In the supplementary information provided with your testimony, you suggest that pharmaceutical companies are not complying with their obligations to conduct Phase IV studies. Yet in a recently published report on the performance of drug and biologic firms in conducting post-marketing (Phase IV) studies, FDA finds that, of the studies concluded between October 1, 2003 and September 20, 2004, no studies were identified where the commitment was not met. Likewise, the study indicates that only 1 percent of the pending studies for NDAs and ANDAs were delayed. Doesn’t this report indicate that pharmaceutical firms are doing a good job meeting their post-marketing study commitments in a timely manner?

Answer 3. Under the Food and Drug Modernization Act (FDAMA) of 1997, the FDA is required to report annually in the Federal Register on the status of post-marketing study commitments made by manufacturers of approved drug and bio-

logical products. The most recent report includes information available through September 30, 2004.¹⁵ The following table summarizes the status of the open post-marketing commitments for New Drug Applications (NDA) and Abbreviated NDAs (ANDA).

Table. Open Post-Marketing Commitments

Status	NDA/ANDA
Pending (study not yet initiated, not delayed)	812 (68%)
Ongoing (proceeding on schedule)	219 (18%)
Delayed (behind schedule)	15 (1%)
Terminated (study ended, no final report submitted)	2 (<1)
Submitted (study ended, final report submitted)	143 (12%)
Total number of open commitments	1191 (100%)

The number of open post-marketing commitments, currently at 1191, remains large (Table). Although 143 (12 percent) were submitted and another 234 (19 percent) were ongoing or delayed, a total of 812 (68 percent) have not yet been initiated. It appears that if these “pending studies” had no “original schedule” at the time of the original agreement to conduct them, they can never be delayed, and some may remain in the “pending” category in perpetuity. The large number of “pending” studies is a concern.

The tardiness with post-marketing commitments can be most clearly illustrated by the accelerated approval mechanism, where the post-marketing studies are essential to defining what, if any, clinical benefit may derive from drugs approved on the basis of surrogate end points. In testimony before the Senate Health, Education, Labor and Pensions Hearing on the “FDA’s Drug Approval Process: Up to the Challenge?” on March 1, 2005 and in a recent article,¹⁶ Dr Fleming raised concerns about the quality and the timing of post-marketing commitments associated with the accelerated approval (subpart H) regulatory process. “One of the more disturbing facts revealed in that meeting (ODAA, March 2003),” writes Fleming, “was that the average time between the granting of marketing through AA [accelerated approval] and the completion of on-going validation trials for these eight products was projected to be 10 years Furthermore, after receiving authorization to market the product, the sponsor often has a loss of the sense of urgency that in the pre-marketing settings is a powerful driving force for the sponsor to obtain timely evaluation of the benefit-to-risk profile of the intervention.”¹⁶ Dagher and colleagues discuss some of the same accelerated-approval cancer drugs in their review.¹⁷ For the 15 cancer drugs that were granted accelerated approval between 1992 and 2004, postmarketing studies that used a clinical outcome were required for full approval, and to date, only 6 (40 percent) of the 15 have met their post-marketing requirements.¹⁷ This leisurely approach to completing post-marketing commitments is not adequate.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY BY BRUCE M. PSATY, M.D.

Question 1. Pharmaceutical manufacturers must pay attention to risk and benefit when designing drugs and deciding what to take to market. Is it appropriate to give them the responsibility for drug safety after marketing?

Answer 1. This approach assigns the fox to guard the hen house. In the case of Baycol (cerivastatin), a lipid-lowering statin drug, the manufacturer was unable to overcome the inherent conflict of interest in interpreting and responding to the adverse event reports that appeared soon after the drug was launched.¹³ Several opportunities were missed to protect patients and prevent injuries. The manufacturer was slow to respond to signals, failed to conduct key safety studies in a timely fashion, decided not to publish a high-dose study with unfavorable findings, and ignored the safety recommendations of its own scientists and epidemiologists.

Soon after the Baycol was on the market, Bayer scientists conducted excellent analyses of the FDA’s MedWatch data. They identified rhabdomyolysis as a major adverse effect of Baycol, used either alone or in combination with Lopid (gemfibrozil). According to a memo from Bayer scientists in March 2000, “The findings [of internal analyses] indicate that in patients receiving monotherapy, cerivastatin substantially elevates risk for rhabdomyolysis compared with other statins. In combination with gemfibrozil, cerivastatin patients were also found to be at a remarkable disadvantage compared with patients receiving gemfibrozil with an-

other statin.”¹³ This information was not, however, communicated to patients, physicians or the FDA.

These safety findings were reported to David Ebsworth, who headed Bayer AG's Pharmaceuticals Business Group. In a memorandum and order regarding the Bayer AG Securities Litigation, District Judge William H. Pauley III summarizes the response to these safety concerns: “On August 2, 2000, senior members of Bayer's Global Drug Safety team and consultants met with Plischke to discuss the accumulation of adverse event reports. A consensus emerged that the data concerning Baycol's dangers ‘was putting the brand at risk.’ When that conclusion was communicated to Ebsworth, he dismissed the reservations of the safety experts and instructed his marketing team ‘to promote the hell out of this product.’”¹² Baycol remained on the market for another year. By 2000, annual drug sales for Baycol were supposed to be several hundred million dollars and were soon expected to reach blockbuster proportions of \$1 billion per year. Ebsworth's one-sided attention to drug sales rather than drug safety delayed the withdrawal of the Baycol and harmed patients. Hence, the need for a strong Center for Marketed-Drug Evaluation and Research to protect the health of the public.

Question 2. You have advocated a separate Center for Drug Safety, within the FDA, for post-market assessments. Why do you feel a separate center is needed? Some seem concerned that a separate safety center would make decisions strictly based on determinations of safety, without considering the benefits of drugs. Is that a valid concern? How might we ensure that all decisions made are both unbiased and based on a weighing of risk against benefit?

Answer 2. The Office of New Drugs dominates CDER. In the last year, safety concerns about antidepressants and COX-2 inhibitors did not find an open forum for expression at the FDA. The report by the Office of the Inspector general points to the fact that “21 percent of FDA respondents indicated that the work environment allowed for the expression of differing scientific opinions to a small or no extent.”³ The current structure and culture at the FDA is just what industry desires—a powerful engine to approve drugs and a weak effort to investigate safety in the post-marketing setting. What the American public needs and deserves, in addition to the rapid approval of drugs, is a Center whose mission is devoted to post-marketing evaluations of the safety and efficacy of marketed drugs.

In a recent commentary, the *JAMA* editors point out the inherent conflict of interest when the OND reviews its own approval decisions: “It is unreasonable to expect the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong (ie, that the decision to approve the product was subsequently shown to be incorrect).”¹⁸ Although a new CMDER would still be within the FDA, the separation of the CMDER from CDER is necessary to assure the independent review of drug safety questions. William Schultz, the FDA's deputy commissioner for policy from 1994 to 1998, agrees: “FDA should separate the monitoring of drugs after they have been approved from the drug review function The post-market function should be separated from the drug review function.”¹⁹

Several key FDA leadership positions have been vacant in recent years. In public statements, some FDA officials have occasionally seemed to lack a public-health perspective on the balance of risks and benefits. For instance, two senior CDER officials called epidemiologic estimates of Vioxx injuries “junk science”²⁰ and claimed that the deaths caused by Vioxx were “not real deaths.”²⁰ As the FDA Advisory Committee indicated in mid February, the COX-2 inhibitors do increase the risk of heart attack and stroke. Tens of thousands of patients were injured, and many died. The CDER leadership has yet to offer an explanation for why the cardiovascular risks of the COX-2 inhibitors remained undetected for so many years. The studies designed by Merck for the approval of Vioxx were individually sound. But as a group, they minimized the possibility of finding cardiovascular harm, which was biologically plausible on the basis of the known actions of Vioxx. The FDA missed an opportunity to protect the health of the public by failing to insist at several stages that the company attend carefully to potential risks as well as benefits. Without an appreciation for the opportunities for prevention that may have been missed, it is not clear that the CDER leadership can avoid future Vioxx-like drug disasters. To protect the health of the public, the FDA needs an independent CMDER whose primary mission, vision and values are geared toward monitoring and assessing the safety and efficacy of drugs that are on the market. Passing the responsibility from CDER to CMDER at the time of approval also avoids the potential conflict of interest mentioned by the *JAMA* editors.

Question 3. Has the FDA done a good job in assessing risk versus benefit for new drugs? How about for approved drugs in the post-marketing setting? Can you explain any similarities or differences?

Answer 3. In the pre-approval setting, the FDA often does a good job of assessing what is reported by the company about the risks and benefits of new drugs. On the basis of the pre-approval studies, however, the FDA often has limited data on the risks and benefits of drugs that will be used long term for chronic conditions such as arthritis. People use arthritis pain medications for many years, but before Vioxx was approved, several thousand patients received the drug usually in small trials that were designed to assess pain relief over the course of a few weeks or months.²¹ Only about 750 patients received usual doses of Vioxx, 12.5 mg or 25 mg per day, for a year or longer. Even though the FDA medical officer observed a three-fold increase in the risk of “thromboembolic events” in short-term studies,²² Vioxx was approved and eventually used by many patients—those with heart disease and those taking aspirin—who had often been excluded from the pre-approval trials. Large long-term clinical trials of drugs that will be used by millions of Americans for many years are best started as early as possible in the drug-approval process. This public-health approach, which need not slow the drug approval process, recognizes and anticipates how the drugs will be used in the population once they are approved.

In the post-marketing setting, some OND decisions seem more industry-friendly than public-health friendly. For instance, in clinical trials of the 0.8 mg supplemental NDA for Baycol, the findings suggested a high likelihood of harm to about 7 percent of thin elderly women.²³ Although the manufacturer needed this dose to compete with Lipitor (atorvastatin), the public-health rationale for approving the 0.8 mg dose, given the known risks, was not clear. Within a year, Baycol was withdrawn from the market because of rhabdomyolysis, a serious adverse event that was especially common at high doses. A second example is Rezulin (troglitazone), a diabetes drug, that was associated with episodes of liver failure and death soon after marketing. The drug was withdrawn from the market rapidly in the United Kingdom.²⁴ In the United States, the FDA and the manufacturer experimented with a series of recommendations and label-revisions that did not work.^{25 26} Rezulin was eventually withdrawn from the U.S. market in 2000.¹ Finally, in the VIGOR trial,²⁷ 50 mg dose of Vioxx was associated with a five-fold higher risk of heart attack than naproxen. With the large number of effective low-risk pain medications then available, it is not clear how the FDA’s formal risk-benefit analysis could have favored keeping the 50 mg dose of Vioxx on the market for the indication of acute pain relief.

The issue is not just weighing risk versus benefit but also the quantity and quality of evidence about risk and benefit. In the post-marketing setting, industry tends to do studies that generate good news for the marketing departments. Those studies, which focus on benefits, are often cleverly designed to generate little useful information about risk. This asymmetry in evidence—well-studied benefits and ill-defined risks—undermines the validity of the knowledge base. In the post-marketing setting, the FDA needs a strong and independent CMDER to pursue aggressively key safety questions that industry would sometimes prefer to ignore. I have not seen this sense of mission from CDER leadership in recent years.

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[Whereupon, at 11:44 a.m., the committee adjourned.]