OFF-LABEL DRUG USE AND FDA REVIEW OF SUPPLEMENTAL DRUG APPLICATIONS

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

HOUSE OF REPRESENTATIVES

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OFF-LABEL DRUG USE AND FDA REVIEW OF SUPPLEMENTAL DRUG APPLICATIONS

THURSDAY, SEPTEMBER 12, 1996

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES AND
INTERGOVERNMENTAL RELATIONS,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 2247, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Souder, Morella, and Towns.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley, professional staff member; Thomas M. Costa, clerk; Ronald Stroman, minority deputy staff director; and Michael Kirby and Cheryl Phelps, minority professional staff members.

Mr. SHAYS. I would like to call this hearing to order and welcome our panelists and our guests as well.

We convene this hearing to examine an important public health issue: the extent and impact of what is known as off-label use of prescription medications.

New drugs are approved or labeled, as safe and effective by the Food and Drug Administration [FDA], for the treatment of certain patients and diseases based on clinical studies conducted by the drug sponsor. After approval, however, new research and the day-to-day practice of medicine often result in the use of a drug for additional indications, additional patients, or at different dosage levels than originally approved.

How prevalent is off-label, or extra-label, drug use? For 50 million children, 40 million cancer patients and 20 million Americans suffering from rare, or orphan, diseases, most of their treatments are off-label. In 1991, the General Accounting Office [GAO], found off-label use of cancer drugs widespread, encompassing a third of all drug dosages to those patients. More than half of the cancer patients in the GAO survey received at least one off-label drug.

As we will hear from our witnesses today, pediatric labeling is also scarce, with up to 80 percent of drugs administered to children prescribed for off-label or unapproved indications. It is estimated that 90 percent of all rare disease treatments are off-label.

While a perfectly legal and necessary part of the healing arts, the widespread off-label use of medicines raises significant public policy and public health issues. Physicians need label information to treat patients effectively. Patients need the same information to make decisions about their own care. Both public and private health care

pairs need safety and efficacy data upon which to base reimbursement policies.

Pervasive off-label use can blur the distinction between medical information and drug promotion, as pharmaceutical developers, with neither financial nor regulatory incentives to undertake costly supplemental studies, find ways to spread the word on off-label uses of their products.

In considering the impact of off-label use, the need for supplementary efficacy information, at least in the form of an FDA approved label, must be balanced against the ability of independent studies and peer-reviewed journals to provide the same data more quickly and effectively than the current FDA supplemental new drug application [SNDA], review process.

The necessity of off-label uses in the private practice of medicine must be balanced against the public health benefits of clinically tested treatment and dosage information for significant patient populations, including children and those suffering from cancers and rare diseases.

The benefits of dissemination of supplemental efficacy and drug use information must be balanced against the need to regulate drug promotion, so treatment decisions are determined by medical, not marketplace, considerations.

We asked our witnesses today to help us gauge the scope and implications of off-label use and to discuss the role of FDA's review of supplemental new drug applications in maintaining the necessary balance between regulation and innovation, between information and promotion, and between individual patient care and public health.

We welcome all our witnesses and look forward to this testimony. I think this is going to be a very interesting hearing and a good introduction for this committee to this very important issue. And whether it is Mr. Towns or I that chair this committee next year, this issue will be pursued.

And now I welcome my ranking member, who has been an equal partner in these hearings over the last 2 years. This is the 49th hearing this committee has held.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by first thanking you for having this hearing and also to say to you that we really appreciate your leadership over the past 2 years. And, of course, I want to let you know a lot of the things you have done, I will do them next year.

The regulation of drug products is an important function of the Food and Drug Administration due to the efforts of the FDA that drugs are safe and effective and that physicians, pharmacists, nurses, and patients are uniformly aware of their appropriate use. Even so, the use of off-label drugs is extraordinarily high. In many instances, these drugs have significant, sometimes life-preserving, value.

There are four principal issues that stem from the use of drugs approved for one purpose but prescribed for another: First, FDA procedures for reviewing supplemental new drug applications have been characterized as necessarily time-consuming and also costly; second, the therapeutic benefits of an off-label drug may be presumed before its safety and efficacy are established; third, reim-

bursement denials for off-label use may prevent patients from receiving the best care available; fourth, pharmaceutical manufacturers cannot promote a drug regardless of its benefits if its use isn't consistent with the FDA-approved label.

This hearing will help us establish the prevalence and implications of off-label drug use. It also provides us an opportunity to assess the efficacy of the FDA's supplemental new drug application review procedures.

The General Accounting Office indicates that the FDA has improved its response to supplemental applications by 71 percent. I would like to know what impact this progress has had on the willingness of the pharmaceutical manufacturers to submit supplemental applications.

I welcome today's witnesses and look forward to hearing their views. Mr. Chairman, I am committed to working with you on this issue and again thank you very much for convening this hearing.

Mr. SHAYS. You are welcome, and I thank my colleague. I understand Mr. Souder doesn't have an opening statement. I would like to say, however, that as vice chairman of this committee, his participation has been extensive throughout the last 2 years and I have learned a lot from his questions. He is really an outstanding member. I know that is what chairmen say about their members, but he is truly an outstanding member.

I understand Mrs. Morella, who has been active on the very issue that we have been involved in and so many others, would like to make a statement.

Mrs. MORELLA. And a truly outstanding member.

Mr. SHAYS. Depends what you say, young lady.

Mrs. MORELLA. Thank you. I don't have an opening statement except to say that, Mr. Chairman, I appreciate your scheduling this very important oversight hearing on FDA reviews of supplemental new drug applications and off-label use of prescription drugs. You are right, I am very interested in it, having the FDA in my district in such a biomedical area, including NIH, National Naval Medical and other medical facilities. Bethesda is truly well named for the "Pool of Bethesda", which had curing qualities.

Off-label use of drugs is increasing and, as we know, the GAO now estimates that between 80 and 100 percent of cancer, pediatric, and rare disease patients use off-label drugs. There are a number of critical questions that need to be addressed today, including the effect of off-label use on public health and the relationship between the FDA approval process for SNDA's and the prevalence of off-label use.

So, Mr. Chairman, these issues need to be addressed. I look forward to hearing the testimony and learning from our witnesses today. Thank you.

Mr. SHAYS. I thank you very much. The only reason why you didn't get an introduction is I think you are pretty well known in this area.

So let me call on our first panel. It is Sarah Jaggar, who is Director of Health Services Quality and Public Health Issues, General Accounting Office [GAO], accompanied by George Silberman, who will also be sworn in and respond to questions if we have them.

And also testifying will be Dr. Joseph DiMasi, who is from Tufts University Center for Drug Development.

We invite all three panelists to come up. We would like to swear you in. If you could remain standing, we will swear you in.

[Witnesses sworn.]

Mr. SHAYS. For the record, our witnesses have responded in the affirmative. I would just like to take care of some housekeeping for the committee.

I ask unanimous consent that all members of the subcommittee be permitted to place any opening statements in the record and that the record remain open for 3 days for that purpose. And without objection, so ordered.

I ask unanimous consent that our witnesses be permitted to include their written statements in the record. Without objection, so ordered.

We will start with the GAO and then we will go to you, Dr. DiMasi. Thank you. We welcome your testimony.

STATEMENTS OF SARAH JAGGAR, DIRECTOR OF HEALTH SERVICES QUALITY AND PUBLIC HEALTH ISSUES, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY GEORGE SILBERMAN, ASSISTANT DIRECTOR; AND JOSEPH DIMASI, TUFTS UNIVERSITY CENTER FOR DRUG DEVELOPMENT

Ms. JAGGAR. Thank you. Good morning, Mr. Chairman and members of the subcommittee. I am pleased to be here to appear before you this morning to discuss off-label drug use and the problems off-label use pose for drug promotion and for advertising. With me is George Silberman, the assistant director who has led our work in this area.

My statement today will cover four points: what off-label use is; the existing evidence on the prevalence and nature of off-label use; the dilemmas posed by off-label use, including the question of whether or not to allow promotion for off-label uses; and two general approaches for how these dilemmas may be resolved.

My comments today are based on our 1991 study of off-label drug use among physicians who specialize in cancer care and on new analyses of FDA performance that we conducted for this hearing. We also interviewed representatives from the American Society of Clinical Oncology, the American Academy of Pediatrics, and the National Organization of Rare Diseases.

To my first point: What is off-label drug use? Physicians use a drug off-label when they prescribe an FDA-approved drug for treatments other than those specified on the label. So that goes to: What is the label? Before marketing a new drug in the United States, the manufacturer must obtain approval from FDA by specifying both the medical conditions the drug is effective against and the patient groups for whom the drug has been shown to be effective. This information is contained in the proposed label submitted by the sponsor.

When FDA approves a new drug application, this approval identifies only the uses for which the manufacturer has demonstrated to FDA's satisfaction substantial evidence of safety and effectiveness. If, later, evidence arises of other safe uses, then the drug's manufacturer can submit a new application to have the label

changed, again demonstrating that the product is both safe and effective for the treatment of the new condition. If FDA agrees, it changes the label to reflect the expanded use.

Second, let me briefly discuss the extent of off-label drug use. Evidence on the extent and types of off-label drug use is limited. Hence, in 1989, we studied drug prescribing patterns among cancer specialists. We found that one-third of all drugs oncologists administered were used off-label. We also found that more than half of the cancer patients, 56 percent, were prescribed at least one drug off-label as part of their chemotherapy regimen.

The extent to which off-label use is prevalent in all areas of medicine is not clear; however, there is evidence it is even more common with AIDS care than for cancer, and it is generally acknowledged that off-label use is extensive for rare diseases and for pediatric populations.

What are the problems posed by off-label drug use? Off-label use is not necessarily inappropriate. FDA acknowledges the potential benefits of off-label use and also recognizes that there are important off-label uses of approved drugs and that physicians need to have access to accurate information about these drugs.

Our analysis shows that the nature of potential problems associated with the drug label has changed. Although in the past the primary concern was with reimbursement denials associated with off-label use, today concern about the off-label use of drugs focuses on the limiting role the label plays in defining appropriate boundaries for drug promotion and advertising. The concern with promotion seems to have grown in direct relation to the increasing competitiveness of the market for pharmaceuticals.

Finally, I would like to offer two general approaches to address the promotion dilemma. Under the first approach, promotion could be based partially or entirely on any of a variety of other sources of information that are commonly accepted as reputable, such as the drug compendia and refereed journals. Legislation currently being considered proposes such an approach.

The benefits of this strategy are that it avoids many of the costs needed to assemble a supplemental application for FDA approval, and it also allows promotion earlier than would be likely if companies had to wait for FDA to approve an efficacy supplement. The limitations, however, are evidenced by those past instances where drugs shown to be effective in published research were later found to be either ineffective or, in some cases, actually harmful for patients.

Another approach is to change the process for updating labels so that it is more timely and more reasonable in its demands for information, thereby making it simpler and possibly less costly to update the label. A concern, however, is the length of time it takes FDA to process drug applications.

Therefore, for this hearing, we looked at FDA's timeliness in responding to efficacy supplements. We found that the average approval time for efficacy supplements has decreased from 19 months in 1993 to 12 months in 1995.

FDA has also made changes in the evidence necessary to obtain approval. FDA instituted a mechanism known as accelerated approval, whereby drugs can receive approval with considerably less

evidence than was traditionally necessary. FDA has already made some changes in the evidence required for certain efficacy supplements and has the discretion to use the same authority to make changes to reviews for other purposes.

In sum, Mr. Chairman, in a 1991 study of physicians who specialize in cancer care, we found that off-label use was a prevalent phenomenon. Currently, the drug industry feels overly constrained by labels in their ability to promote their products. We suggest two general solutions to this problem: Relying on sources in addition to the labels to define appropriate promotion and/or making improvements in the process for updating the label.

This concludes my statement. We will be happy to answer any questions you or the subcommittee may have.

[The prepared statement of Ms. Jaggar follows:]

Mr. Chairman and Members of the Subcommittee:

We are pleased to appear before you this morning to discuss the general area of off-label drug use and the more specific problem off-label use poses for drug promotion and advertising. This area is critically important in ensuring the quality of health care, controlling expenditures, and maintaining a viable pharmaceutical industry.

My statement will set this important policy issue in context, by covering four points: (1) what "off-label" use is; (2) the existing evidence on the prevalence and nature of off-label use; (3) the dilemmas posed by off-label use, including the question of whether or not to allow promotion for off-label uses; and (4) two general approaches for how these dilemmas may be resolved.

My comments today are based on our study of off-label drug use among physicians who specialize in cancer care that was published in 1991 and on new analyses of FDA performance that we conducted expressly for this hearing.[1]

In sum, we found that off-label use is a prevalent phenomenon that has presented different problems for policy-makers at different times. As it stands now, the problem is that the drug

[1]U.S. General Accounting Office, Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies, GAO/PEMD-91-14 (Washington, D.C.: September 1991).

industry feels overly constrained by labels in its ability to promote its products. This problem can be solved either by relying on sources in addition to the label to define appropriate promotion or by making improvements in the process for updating the label. These two options are not necessarily mutually exclusive and both have benefits and drawbacks.

DRUG LABELING AND OFF-LABEL DRUG USE

Amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act of 1962 mandated that FDA evaluate the safety and effectiveness of all new drugs. Before marketing a new drug in the United States, the manufacturer (also called the "sponsor") must obtain approval from FDA by specifying both the medical conditions the drug is effective against and the patients groups for whom the drug has been shown to be effective. This information is contained in the proposed "label" submitted by the sponsor. It is the sponsor's responsibility to assemble all the evidence that would support the uses proposed in the label.

When FDA reviews the sponsor's evidence for the drug's safety and efficacy, it does so primarily for the conditions specified in the sponsor's proposed label. Therefore, when FDA "approves" a new drug application, this approval identifies only the uses for which the manufacturer has demonstrated to FDA's satisfaction substantial evidence of safety and effectiveness.

If, after FDA has approved a drug, evidence arises of its safety and effectiveness in treating conditions or patient groups other than those named in the label, then the drug's manufacturer (or any other interested party) can submit a new application to have the label changed. This application, known as an "efficacy supplement," is similar to the original application in that it must contain evidence demonstrating to FDA's satisfaction that the product is both safe and effective for the treatment of the new condition. If FDA agrees with the sponsor's claims in the supplemental application, the agency changes the label to reflect the expanded use that the applicant has requested.

Physicians use a drug "off-label" when they prescribe an FDA-approved drug for treatments other than those specified on the label.[2] According to FDA,

> "the legislative history of the FD&C Act indicates that the Congress did not intend FDA to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient

[2]Other terms used to describe the use of medical products for conditions other than those specified on the label include "unapproved," "unlabeled," or "extra-label" use.

populations that are not listed on the FDA-approved labeling."[3]

PATTERNS OF OFF-LABEL DRUG USE

The evidence on the extent and types of off-label drug use has not been extensive. Almost a decade ago, a University of Washington Family Medicare Center study found that off-label use was relatively rare: only 46 drugs of the 500 that were evaluated were being used in an off-label context. However, assertions by a group representing community cancer care centers presented a very different picture.[4] In 1989, in an effort to document the amount and types of off-label use, we initiated a study of drug-prescribing patterns among cancer specialists. By examining the drugs oncologists prescribed for specific types of cancer, we determined that one third of all drugs they administered were used off-label. Further, of the 46 approved anticancer drugs and hormonal agents prescribed by oncologists at the time, 44 were prescribed at least once to treat an off-label indication. Perhaps most significant was our finding that more than half of the cancer patients (56 percent) were prescribed at least one drug off-label as part of their chemotherapy regimen.

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[3]Statement by William B. Schultz, Deputy Commissioner for Policy, FDA, before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

[4]Throughout the late 1980s, the Association of Community Cancer Centers issued a series of reports saying that off-label use was prevalent among its participating institutions.

The extent to which off-label use is prevalent in all areas of medicine is not clear. However, there is evidence that it is even more common within AIDS care than for cancer. In a study published earlier this year, researchers from California reported that more than 80 percent of AIDS patients received at least one drug off-label as part of their treatment and that 40 percent of all drugs that were given were provided off-label.[5] Further, it is generally acknowledged that off-label use is also extensive for pediatric populations.[6] This may well stem from a hesitancy to conduct medical experiments on children. Even if these were the only areas where off-label use was common, the number of patients affected would be considerable.[7]

PROBLEMS POSED BY OFF-LABEL DRUG USE

While it may appear to be problematic that many physicians prescribe medications for conditions for which there has been no official determination of safety and benefit, off-label use is

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[5]Carol L. Brosgart et al., "Off-Label Use in Human Immunodeficiency Virus Disease," Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 12:1 (May 1, 1996), 56-62.

[6]The American Academy of Pediatrics claims that 80 percent of drugs administered to children are given off-label. The latest evidence supporting this claim was recently published: Leona Cuttler et al., "Short Stature and Growth Hormone Therapy," Journal of the American Medical Association, 276:7 (August 21, 1996), 531-37.

[7]For example, more than 1 million patients are diagnosed with cancer each year.

not necessarily inappropriate. In fact, a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease. This seemingly anomalous situation can arise when research conducted subsequent to FDA approval shows the drug's effectiveness in treating other conditions, yet the label remains unrevised.[8] For example, this occurred with some frequency in the cancer area where drugs that had been approved for one form of cancer were subsequently shown to have efficacy against other cancers, yet the label remained unchanged.

FDA acknowledges the potential benefits of off-label use. The agency has stated that "under certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice."[9] FDA also recognizes that there are important off-label uses of approved drugs and that physicians need to have access to accurate information about these drugs. This being so, why does evidence of extensive off-label use present a problem?

Our analysis shows that the nature of potential problems associated with the drug label have changed. At the time we collected the data on off-label drug use (spring 1990), the

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[8]Efficacious uses of the drug can remain off the label for a variety of reasons: (1) a supplemental application was not submitted; (2) FDA did not feel the evidence in the application was sufficient to warrant a change in the label; and (3) FDA is still reviewing the supplemental application.

[9]Schultz, cited above.

primary concern was with reimbursement denials associated with off-label use. We found that denials made because the FDA label did not include the specific drug were certainly prevalent. More than half of all the cancer physicians we surveyed reported problems with reimbursement for off-label use, and most indicated that the problems had gotten worse in recent years. Most troubling was that many respondents said they altered what they believed to be optimal therapy in response to these reimbursement denials. In fact, 62 percent of physicians responding to our survey said that they had admitted to hospitals patients who did not require hospitalization solely as a way to circumvent problems with reimbursement denials.[10]

While reimbursement concerns were the primary ones associated with the drug label in the earlier part of this decade, this issue seems to have declined significantly since that time. This decline has been attributed to legislation in 1993 that required Medicare carriers to rely on sources in addition to the FDA-approved label in making reimbursement decisions for cancer therapy. Subsequently, the insurance industry generally followed suit. This is to say not that there are no longer any reimbursement problems with off-label drug use--just that they seem to be more isolated.

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[10]Reimbursement for a hospital stay is based on the condition for which the patient is admitted and not on the basis of which drugs are given.

In recent years concern about the off-label use of drugs has resurfaced. This time the focus is on the limiting role the label plays in defining appropriate boundaries for drug promotion and advertising.[11] Although definitive evidence of a cause-and-effect relationship is difficult to obtain, the concern with promotion seems to have grown in direct relation to the increasing competitiveness of the market for pharmaceuticals. As changes in health care brought on by managed care and other attempts at cost containment have accelerated, pharmaceutical manufacturers have faced a more competitive environment. With increasing competition, it is in the interest of manufacturers to demonstrate as many benefits for their products as possible. The need to impress prospective clients of the value of drugs may be especially true with respect to pharmacoeconomic benefits, in which formulary managers are understandably interested.[12]

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[11]The issue has alternatively been discussed as the desire to promote products more broadly and the need to inform physicians more fully about drugs. Physicians currently gain access to information about off-label uses through compendia, journal articles, continuing medical education programs, symposia, and professional meetings. They also have access to a number of databases that provide information about off-label uses. None of these sources of information is limited by what is contained on the FDA-approved label. Further, a manufacturer can supply physicians with information about off-label uses if the physician specifically requests such information. However, the manufacturer cannot provide information on off-label uses without such a request.

[12]A formulary is a list of drug products. The basic types are "open" formularies, which list the drugs that are recommended but do not restrict physicians in their prescribing behavior, and "closed" formularies, which specify the drugs that physicians can prescribe and, by omission, drugs that they cannot provide to patients.

GENERAL APPROACHES TO ADDRESS THE PROMOTION DILEMMA

Two approaches exist for resolving the dilemma of whether and how widely to allow promotion of off-label uses. One is to rely less on the label as the determinant of what can and cannot be said about a product. The other is to improve the process for updating drug labels.

Change Restrictions Associated With the Label

Under one approach, promotion could be based partially or entirely on any of a variety of other sources of information that are commonly accepted as reputable, such as the drug compendia and refereed journals. The Congress used this strategy for dealing with the previous off-label "crisis," that of reimbursement denials. In the Omnibus Budget Reconciliation Act of 1993, the Congress defined the term "medically accepted indication" to include not only the conditions incorporated in the FDA-approved label but also uses

> "supported by one or more citations which are included (or approved for inclusion) in one or more of the following compendia: the American Hospital Formulary Service--Drug Information, the American Medical Associations--Drug Evaluation, the United States Pharmacopeia--Drug

Information, and other authoritative compendia as identified by the Secretary."

Further, reimbursement could also be based on supportive clinical evidence in peer-reviewed medical literature appearing in publications that have been identified by the Secretary of Health and Human Services. Legislation currently being considered (H.R. 3199) proposes a conceptually similar approach with respect to promotion of off-label drug uses.

This strategy has both benefits and limitations. The benefits are that (1) it avoids many of the costs needed to assemble a supplemental application for FDA approval and (2) it allows promotion earlier than would be likely if companies had to wait for FDA to approve an efficacy supplement.

However, relying on sources other than the label for defining appropriate promotion also has its drawbacks. Most importantly, in instances in the past, drugs that had been shown to be effective in research that was published in respected peer-reviewed journals were later found to be either ineffective or, in some cases, actually harmful for patients.

Change the Process for Updating the Label

Another approach to reducing the barriers to promotion faced by

pharmaceutical companies is to encourage changes in the process for updating labels so that it is more timely and more reasonable in its demands for information. Expediting the review process for efficacy supplements would make the information on labels more reflective of the most current understanding of a drug's benefits, while modifying the information needed to obtain a supplemental approval, could well reduce the costs and disincentives of submitting an application for approval. A process that produced an up-to-date label would benefit all who sell, buy, prescribe, and use drugs.

Although there are benefits to changing the process, the Congress did not choose to do so in response to the problems created when insurers refused to reimburse for off-label uses. This may be the result of the perception that FDA takes an inordinate amount of time to process applications and is unwilling to adapt to an increasingly dynamic environment. Also, any demands that FDA reduce the amount of time it takes to make decisions might result in increased resources for the agency in an era of growing sensitivity about the costs of government.

However, since the time of our work on off-label drugs, much has changed at FDA. One change is that the agency has improved its performance in processing drug applications. In October 1996, we reported that the time to reach decisions on new drug

applications had declined by more than 40 percent.[13] In preparing for this hearing, we also looked at FDA's timeliness in responding to efficacy supplements. Our findings are shown in table 1.

Table 1: Approval Times for Efficacy Supplements in Months, Fiscal Years 1993-95

Year of submission	Number of submissions	Percent approved	Median approval time	Average approval time
1993	69	57%	18	19
1994	67	63	14	14
1995	48	71	12	12

As can be seen from the table, how long it takes for FDA to approve efficacy supplements has been reduced considerably. This improvement is consistent with that found for new drug applications and with the goals established under the Prescription Drug User Fee Act of 1992. Under this act, FDA is held accountable for rapid action on efficacy supplements in the same way that it is accountable for processing new drug applications. The user fee legislation has the added dimension of providing FDA with additional resources so that shorter action times become more realistic goals.

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[13]U.S. General Accounting Office, FDA Drug Approval: Review Time Has Decreased in Recent Years, GAO/PEMD-96-1 (Washington, D.C.: October 1996).

FDA has also made changes in the evidence necessary to obtain approval since the time of our off-label drug study. Largely in response to pressures from patient groups eager to have potentially life-saving drugs available as quickly as possible, FDA has instituted "accelerated approval," a means by which drugs can receive approval with considerably less evidence than was traditionally necessary. FDA has already made some changes in the evidence required for certain efficacy supplements and is considering more far-reaching changes.

Although the changes in FDA review time and in the evidence requested by the agency are promising indicators that labels will become more reflective of a drug's true benefit, the process of updating a label is a collaborative one that involves the sponsor of the application as well as FDA. Therefore, a major limitation of relying on changes in the way FDA reviews efficacy supplements as the solution to the off-label promotion problem is that the agency cannot act on drugs for which supplemental applications are not submitted. If companies remain hesitant to submit supplemental applications, changes in the process at FDA would have little effect on the utility of the label.[14]

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[14]For example, the expiration of a patent on a drug may well remove much of the incentive that a sponsor might have for incurring the costs of the research necessary to support an efficacy supplement for that drug.

Mr. Chairman, this concludes my statement. I would be happy to answer any questions that the Subcommittee might have.

For more information about this testimony, please call George Silberman, Assistant Director, at 202-512-9226. Other major contributors include Michele J. Orza and Thomas J. Laetz.

(108292)

Mr. SHAYS. Thank you very much. Dr. DiMasi.

Mr. DIMASI. Mr. Chairman and members of the subcommittee, thank you for the opportunity to speak today. In a number of studies published over the last decade, my center has tracked approval times for new indications and compared them to the time spent to approve the applications for the drugs' original uses.

The central hypothesis posited in these studies was that, on average, new uses would be easier to review because most issues or concerns regarding toxicology, chemistry and manufacturing would have been addressed in the original review. This reasonable hypothesis leads to the expectation that supplemental indications would, on average, be approved more quickly than the original uses.

Surprisingly, none of these studies supported this expectation. For the most recent period analyzed, 1989 to 1994, supplemental indication approval times averaged 28.3 months, which was 3.7 months longer than the average for the original indications. The difference between the SNDA and NDA approval times was statistically significant.

A closer look at the data for this period, however, does show some improvement for the last 2 years. The average SNDA approval times for 1993 and 1994 were 2.8 and 3.6 months shorter, respectively, than the NDA approval times for the drugs for which the new uses were approved. The differences, however, were not statistically significant. Overall, the evidence on approval times cannot be used to support a case for quicker approval of new indications relative to the original indications.

Many new uses for old drugs offer significant advances in patient care. In some cases, the follow-on indication is even more important than the original use. In our most recent study of the supplemental indication approval process, we also examined the approval times for new uses that were recognized by the FDA as representing important advances. Although our data indicate that, other things being equal, those new uses that the FDA had noted were important were approved more quickly than other new uses, the approval times for the important new uses averaged about 10 months longer than the average approval time for the original indications. This difference was statistically significant.

The data that we analyzed in our studies did not allow us to definitively assess the impact of the User Fee Act on the supplemental indication process. Recent user fee statistics released by the FDA on efficacy supplements, though, are encouraging. The reported statistics are, however, for FDA actions on applications which include issuing not-approvable and approvable letters; thus, they do not measure the time from initial submission of an SNDA to approval. The category of efficacy supplements is also much broader than the types of applications that we have analyzed in the past, which were those for new indications and new patient groups.

Providing sufficiently strong incentives for firms that file supplements on some well-established off-label uses while also encouraging reimbursement for these uses is a difficult problem to resolve. A number of process and legislative measures can, however, be considered that potentially could facilitate the development and use of

safe and effective new uses. I will mention a few. And by a new use, I mean here either a new indication or a new patient group.

Third party review. Although a formal report has never been issued, by all appearances, the so-called MITRE experiment was a success. This pilot project involved the outside expert review of five efficacy supplements. The reviews were conducted expeditiously—2 to 4 months per supplement for the biostatistical and medical reviews. They were not excessively expensive and the quality of the reviews was high, as judged by the fact that the FDA concurred with MITRE's recommendations for all five supplements. Additionally, not all of the recommendations were favorable. The current user fee legislation prohibits the use of user fee revenues for outside reviews, but this problem can be remedied legislatively. Faster reviews will increase the incentives to pursue labeling approval.

Paper SNDA's. Greater use and acceptance of so-called paper SNDA's should be encouraged. In some cases, the published literature can serve as the basis for approval of off-label uses. This obviates the need for extensive and expensive additional clinical testing and reduces the time needed to get new uses on the product label.

Submissions by nonprofit organizations. In cases where the financial incentives to pursue approval of paper SNDA's are not sufficient to induce firms to seek approval, nonprofit institutions such as patient groups could conceivably put together the information needed for a paper SNDA and petition for approval of the unlabeled use. In these cases, marketing exclusivity would not be granted to the manufacturer.

Expansion of marketing exclusivity. In cases where additional clinical testing must be done but patent protection has been lost or will soon be lost, an additional period of marketing exclusivity conceivably could be granted to the firm that obtains the approval. Currently, firms can acquire 3 years of marketing exclusivity for a new use, a period during which only the firm that obtained the approval is allowed to promote its product for the approved new use.

With regard to reimbursement. To ameliorate access problems for off-label uses, extra FDA expert panels could be set up by one or more of the pharmaceutical compendia, distinguished professional societies, or the Institute of Medicine, for example, to review unlabeled uses that are supported by evidence. Third party payers would then have a recognized basis for reimbursing off-label uses that are viewed authoritatively as acceptable medical practice. Finally, programs organized by professional societies can be developed to educate physicians about the optimal use of drugs for unlabeled indications prior to labeling approval.

In conclusion, it is imperative that we have an efficient approval process for new indications and that third party payers recognize legitimate new uses even before they reach the label. Under the user fee program, the FDA appears to have made substantial progress in achieving quicker reviews of applications for both original and follow-on indications. The agency has also recognized the problems associated with important off-label uses and has encouraged firms to submit SNDA's for these uses. We need, however, I believe, to examine additional means to achieving the ends that we all desire.

Thank you.

[The prepared statement of Mr. DiMasi follows:]

Written Testimony of Joseph A. DiMasi, Ph.D.
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House Subcommittee on Human Resources and Intergovernmental Affairs
Committee on Government Reform and Oversight
U.S. House of Representatives
September 12, 1996

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to speak to the Committee. My name is Joseph DiMasi. I am Director of Economic Analysis at the Tufts Center for the Study of Drug Development, a non-profit, policy research group affiliated with Tufts University. The opinions that I express here are my own and do not necessarily reflect the views of the Tufts Center for the Study of Drug Development.

In this testimony I will present historical data on the length of the supplemental indication approval process and discuss potential solutions for getting off-label uses approved expeditiously. The information relied upon in this testimony was obtained from Tufts Center for the Study of Drug Development (CSDD) databases that track drug development and approval times for new chemical entities (NCEs) approved in the United States since 1963.

Comparisons of Approval Times for Supplemental and Original Indications

The time that it takes to get new uses for old drugs approved is an important topic for analysis for at least two reasons. The longer the approval process, the longer some patients will wait for treatment simply because not all physicians will be aware of the effectiveness of the drug in its new use. Secondly, use of a drug for an off-label use may be curtailed if third-party payers refuse to reimburse for unapproved uses.

In a number of studies published over the last decade, the CSDD has tracked approval

times for new indications and compared them to the time spent to approve the applications for the drugs' original uses published over the last decade.[1-3] The central hypothesis posited in these studies was that, on average, new uses would be easier to review because most issues and concerns regarding toxicology, chemistry, and manufacturing would have been addressed in the original review. This reasonable hypothesis leads to the expectation that supplemental indications would, on average, be reviewed more quickly than would the original uses. Surprisingly, none of these studies have supported this expectation.

Although for some of the early periods analyzed in these studies average supplemental new drug application (SNDA) approval times were less than the average times to approve the original uses of these drugs, the differences were not statistically significant. For the more recent periods analyzed, however, approval of SNDAs took longer on average than did the original new drug applications (NDAs). As shown in Figure 1, the average approval time for supplemental indications approved during 1984 to 1988 was 4.9 months longer than the average approval time for the original indications of those drugs that had new uses approved during this period. For the most recent period analyzed, 1989 to 1994, supplemental indication approval times averaged 28.3 months, which was 3.7 months longer than the average for the original indications. The differences between SNDA and NDA approval times for these two periods were statistically significant.

A closer look at the data for the most recent period, however, does show some improvement for the last two years. As shown in Figure 2, the average SNDA approval times for 1993 and 1994 were 2.8 and 3.6 months shorter than the NDA approval times of the drugs for which the new uses were approved. However, as was the case for earlier periods, the

differences were not statistically significant. Overall, the evidence on approval times cannot be used to support a case for quicker reviews of new indications.

Many new uses for old drugs offer significant advances in patient care. In some cases, the follow-on indication is even more important than the original use. Our most recent study of the supplemental indication approval process examined the approval times for new uses that were recognized by the FDA as representing important advances. These new uses include AZT for pediatric patients with symptomatic HIV disease, tamoxifen for women with auxiliary node-negative breast cancer, and pentostatin for untreated hairy cell leukemia.

For approvals through 1993, the FDA has indicated in its publications those new indication approvals that it considered to be significant improvements in patient care. Figure 3 shows the mean approval times by year from 1989 to 1993 for those follow-on indications that were noted by the FDA to be important and compares them to the mean approval times for the original indications of those drugs that had received the supplemental indication approvals. Although our data indicate that, other things being equal, those new uses that the FDA had noted were important were approved more quickly than other new uses, the approval times for the important new uses averaged about 10 months longer than the average approval time for the original indications. This difference was statistically significant.

The data that we analyzed in our studies did not allow us to definitively assess the impact of the *Prescription Drug User Fee Act of 1992*[4] on the supplemental indication process. Recent user fee statistics released by the FDA on efficacy supplements are encouraging.[5] The reported statistics, however, are for FDA actions on applications, which include issuing not-approvable and approvable letters. Thus, they do not measure the time from initial submission

of an SNDA to approval. The category of efficacy supplements is also much broader than the types of applications that we have analyzed (new indications and new patient groups). Efficacy supplements include, for example, new dosage regimens and new routes of administration, as well as new indications, new patient groups, and other types of supplements. The FDA data and our results suggest that there have been improvements in recent years in approval times for follow-on uses, but the need for further improvement remains.

Potential for Encouraging and Facilitating the Inclusion of New Uses on Product Labels

Why has approval of follow-on indications generally taken so long? A likely explanation for our results is that historically the agency had effectively placed a low priority on supplemental filings, because the drugs were available in the marketplace and physicians can, and often do, prescribe for off-label uses. Such a perspective would not be problematic if the information available to all physicians were sufficiently complete to allow their prescribing to be optimal and if reimbursement were never conditioned on whether an indication is FDA-approved. However, the restrictions placed on manufacturers on dissemination of information about off-label uses suggest that there will be some underuse or misuse of drugs. For example, a recent study found that approved new indications appeared in one of the major pharmaceutical compendia (United States Pharmacopeia - Drug Information), on average, 2.5 years prior to FDA approval.[6] Optimal use of drugs is also impaired when third-party payers refuse to reimburse for uses of a drug that are not included in an FDA-approved label.[7]

Patient care can be enhanced when applications for supplemental indications are approved expeditiously and when reimbursement is routinely allowed for off-label uses that are

supported by the scientific literature. However, establishing sufficiently strong incentives for firms to file supplements on some well-established off-label uses, while also encouraging reimbursement for these uses, is a vexing problem. For a manufacturer to invest in the expensive clinical trial work that is needed for many supplemental filings the perceived benefits must exceed the costs. If a substantial period of patent protection for the drug remains, then the weighing of benefits and costs may well be tipped in favor of pursuing FDA approval. However, if patents have expired or are close to expiration, then the three years of marketing exclusivity and the expansion of the market for the drug that will come with FDA approval may not be enough to induce the firm to seek approval, since generic substitution can be expected to capture a significant portion of the extra revenues that will be generated. Any measures that reduce the costs or increase the benefits of getting new uses approved will increase the incentives for manufacturers to pursue approval of new indications.

A number of process and legislative measures that potentially could facilitate the development and use of safe and effective new indications should be considered.

- **Third Party Review**. Although a formal report has never been issued, by all appearances the MITRE experiment was a success. This pilot project involved the outside expert review of five efficacy supplements. The reviews were conducted expeditiously (two to four months per supplement for the biostatistical and medical review), they were not excessively expensive, and the quality of the reviews was high, as judged by the fact that the FDA concurred with MITRE's recommendations for all five supplements.[8] Additionally, not all of the recommendations were favorable. The current user fee legislation prohibits the use of user fee revenues for outside reviews,

but this problem can be remedied legislatively. Faster reviews will increase the incentives to pursue labeling approval.

- **Paper SNDAs.** Greater use and acceptance of so-called paper SNDAs should be encouraged. In some cases, the published literature can serve as the basis for approval of off-label uses. This obviates the need for extensive and expensive clinical testing and reduces the time needed to get new uses on the product label.
- **Submissions by Non-Profits.** In cases where the financial incentives to pursue approval of paper SNDAs are not sufficient to induce firms to seek approval, non-profit institutions, such as patient groups, could put together the information needed for a paper SNDA and petition for approval of the unlabeled use. In these cases, marketing exclusivity would not be granted to the manufacturer.
- **Expansion of Marketing Exclusivity.** In cases where additional clinical testing must be done but patent protection has been lost or will soon be lost, an additional period of marketing exclusivity can be granted to the firm that obtains the approval. Currently firms can acquire three years of marketing exclusivity for a new use, a period during which only the firm that obtained the approval is allowed to promote its product for the approved new use.
- **Consistent Reimbursement.** To ameliorate access problems for off-label uses, extra-FDA expert panels can be set up by one or more of the pharmaceutical compendia, distinguished professional societies, or the Institute of Medicine to review unlabeled uses that are supported by evidence. Third-party payers would then have a recognized basis for reimbursing off-label uses that are viewed authoritatively as acceptable

medical practice.

- **Educational Efforts**. Programs organized by professional societies, such as the AMA, can be developed to educate physicians about the optimal use of drugs for unlabeled indications prior to labeling approval.

Conclusions

In conclusion, it is well accepted that some approved follow-on indications are more medically important than the original indications, and that there is widespread use of already-approved drugs for uses that are not on the product label. Optimal patient care requires that physicians be informed about all of the effective treatments that are available for their patients. It is imperative therefore that we have an efficient approval process for new indications and that third-party payers recognize legitimate new uses even before they reach the label. Under the user fee program, the FDA appears to have made substantial progress in achieving quicker reviews of applications for both original and follow-on indications. The agency has also recognized the problems associated with important off-label uses and has encouraged firms to submit SNDAs for these uses. We need, however, to examine additional means to achieving the ends that we all desire.

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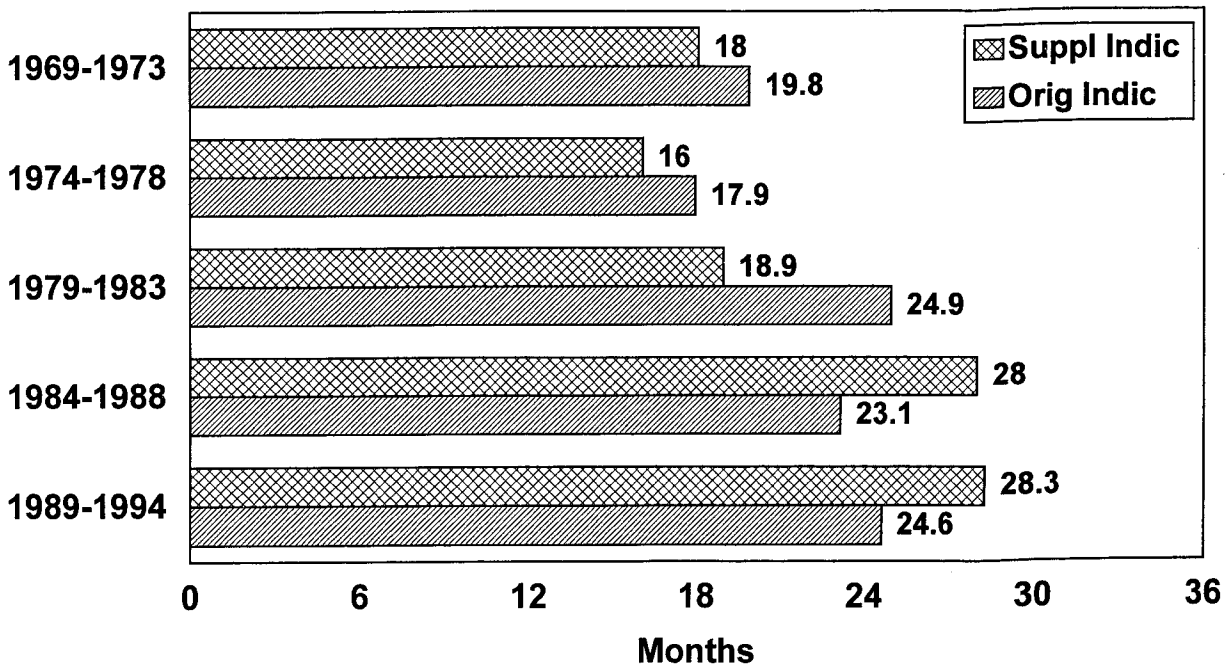
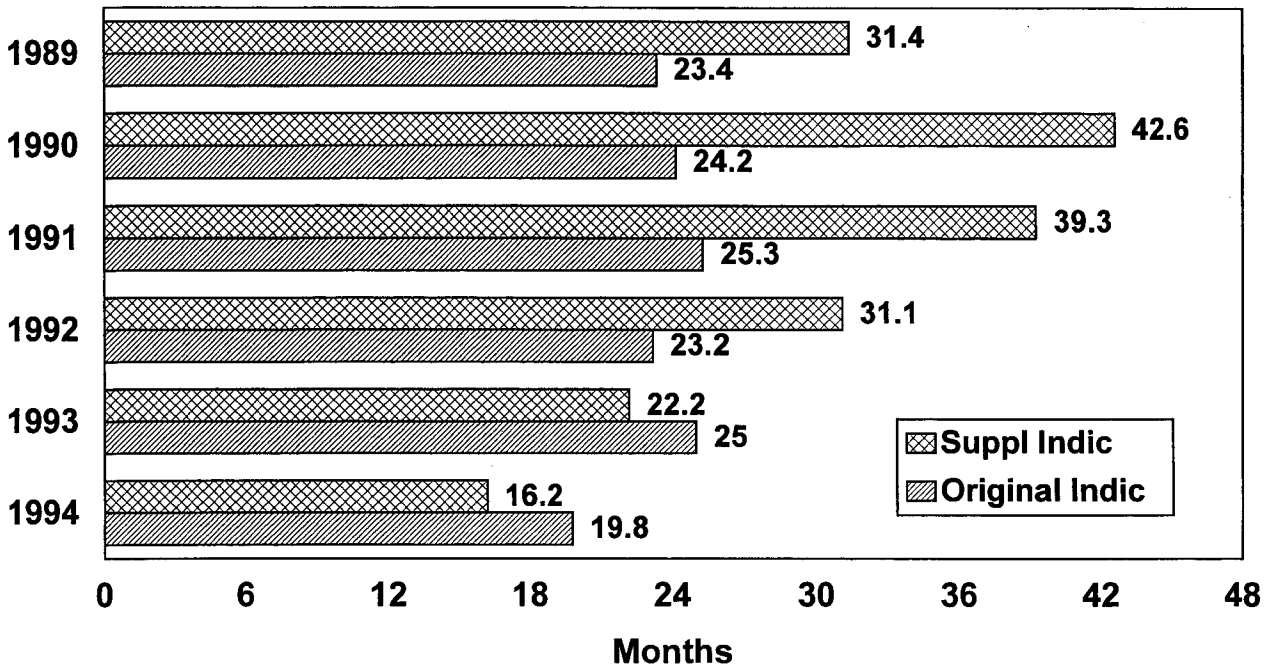
Figure 1. Mean Review Times for Supplemental Indications and for their Associated Original Indications



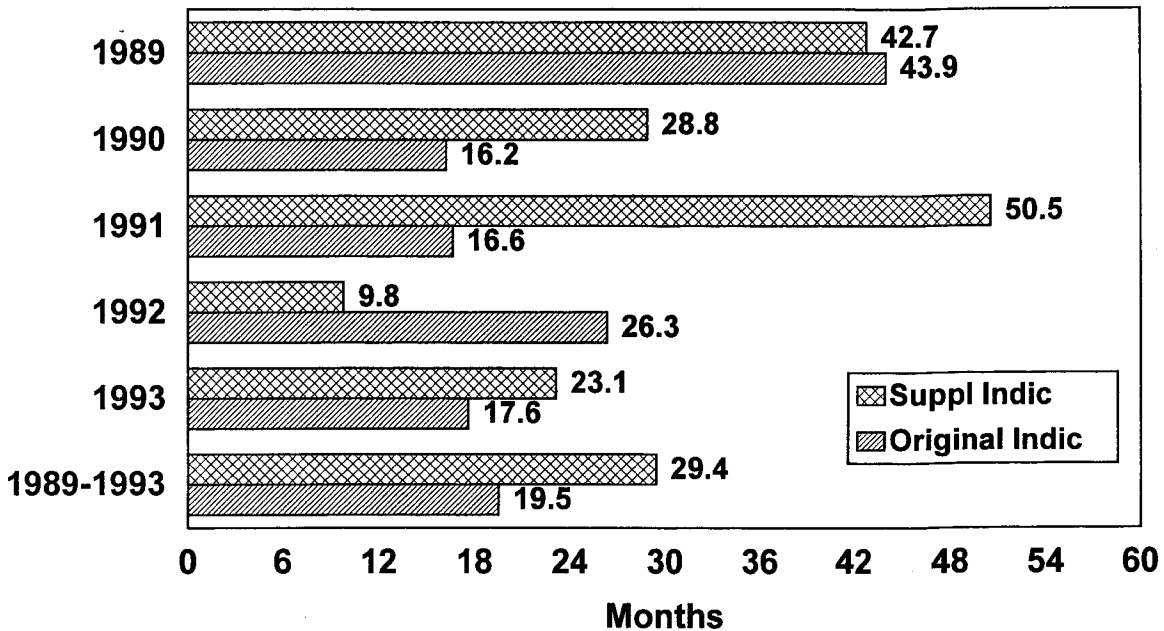
Source: DiMasi *et al.*, *Drug Inf J*, 1996, 30(2):315-337.

Figure 2. Mean Review Times for Supplemental Indications and for their Associated Original Indications



Source: DiMasi *et al.*, *Drug Inf J*, 1996, 30(2):315-337.

Figure 3. Mean Review Times for Significant Supplemental Indications and for their Associated Original Indications



Source: DiMasi *et al.*, *Drug Inf J*, 1996, 30(2):315-337.

Mr. SHAYS. Doctor, thank you very much. It is a very interesting issue and I look forward to hearing your response to some of the questions. This is probably going to be more general in its focus since this is the first hearing on this issue, and it is certainly somewhat of a new issue to me.

With that, Mr. Souder, I will have you start the questioning.

Mr. SOUDER. Thank you. I wanted to first ask Dr. DiMasi, in the different suggestions you had here—the third party review, the paper SNDA's, nonprofits, expansion of marketing exclusivity and consistent reimbursement—what are some of the resistances, or what would they be, to those changes? Is it going to be FDA? Is it going to be the individual drug companies? Maybe you could go through some of those because they sound like pretty reasonable proposals.

Mr. DIMASI. Well, with regard to paper SNDA's, it should be noted that it certainly would not be appropriate in all cases. It would be appropriate in a limited number of cases.

Mr. SOUDER. You say a greater use?

Mr. DIMASI. Pardon me?

Mr. SOUDER. I think you said here a greater use of it.

Mr. DIMASI. Right.

Mr. SOUDER. Not universal, but a greater use.

Mr. DIMASI. Right; absolutely.

Mr. SOUDER. So is there a resistance to a greater use? Why would there be any resistance to that? Are some of the studies funded by certain companies? Is there a question on the accuracy of the studies or just that that's not the way it historically has been done? What would be some of the reasons?

Mr. DIMASI. Well, historically, it has not been done very often. The agency would naturally want to tread very carefully in this area and not want to make mistakes and, indeed, would seek, would desire, optimally definitive information. But, obviously, some tradeoffs would have to be made.

Mr. SOUDER. What would be some potential standards? Because you said you wouldn't have it universally be done. You would use it greater; that they would like to, obviously, have complete control of the experiments, which they wouldn't have in this case. So what would be some criteria to expand that use that would be reasonable?

Mr. DIMASI. Well, I am perhaps, being an economist, not the best person to discuss or establish criteria for acceptance of published medical literature.

Mr. SOUDER. OK, I was more looking for general. So you would like to see it, but that would need to be researched and we would need to have somebody else come in.

Mr. DIMASI. Yes.

Mr. SOUDER. On the nonprofits, has that been done before where people with a patient group have pulled together and petitioned?

Mr. DIMASI. Not to my knowledge.

Mr. SOUDER. Has that ever been run by FDA or do you know if that has ever been considered?

Mr. DIMASI. I have never seen anything, formally put out in that regard, either discussed or written.

Mr. SOUDER. What percentage, knowing that I am asking you specific questions that may be beyond your scope, but what percentage do you think would fall into—you suggest that some of these drugs' secondary uses don't make enough money for the companies to pursue, and that is why you suggested nonprofits. Others, if they received a longer period of time, would change the financial incentives, as opposed to those where there are currently financial incentives enough that they would petition, but that is the group that is taking a long time.

Of those three, do you have any idea what percentage falls in the different categories?

Mr. DIMASI. I have no data on that. I couldn't give you any figures.

Mr. SOUDER. Ms. Jaggar, in your testimony, you suggested that the concern has moved from the reimbursement question more to a health-related question and whether there are adequate and accurate prescriptions being given; whether, in fact, with promotion either from—you didn't say this per se but it was certainly there—that if a company promotes it aggressively to physicians, they may use it more or use it in ways that may not necessarily be tested because they don't have an independent test and they are dependent upon the combination of journals, word of mouth, and the people who come in to promote the drugs to them, and, also, any patients who may have heard about it either from other patients or another place and don't want to be denied it, and so that may be driving the prescription.

How serious a problem is that, both from a health risk and a cost-driven?

Ms. JAGGAR. Mr. Souder, the reimbursement issue does seem to have resolved itself in the past—given that legislation in late 1993 enabled the Medicare Program to consider drugs that had off-label uses if there were reputable sources that they could base the coverage and reimbursement decisions on. Medicaid also. And that is one reason that the reimbursement issue has diminished a bit in terms of its importance.

Mr. SOUDER. But that is reimbursement from the patient's perspective?

Ms. JAGGAR. Right.

Mr. SOUDER. Not necessarily from the Government's or from the company's perspective?

Ms. JAGGAR. Right. The reason that was important from the patient's perspective is that if you couldn't get reimbursement for something, then you have much less access to that drug.

Mr. SOUDER. Right; I understand.

Ms. JAGGAR. What we are seeing in the changing health environment today is that pharmaceutical companies usually, or much more often, are marketing to a larger entity that is making a decision that affects many different physicians. For example, say that a company is marketing to a managed care organization and that managed care organization has established a formulary. In that formulary, they may choose among the seven drugs that would be acceptable to treat a particular disease.

For economic reasons, the formulary of the managed care organization may select a particular drug and, of course, the pharma-

ceutical company would like it to be their drug. So there is additional pressure on the competitiveness of the health industry now as a result. Most formularies have an "out clause" in case a particular drug that is selected doesn't work well for an individual patient, but it requires some additional effort.

That can have an influence on individual patients. If a patient for years has been receiving a particular kind of drug, joins an HMO, and now the formulary doesn't cover that particular drug, there can be some need for adjustment. I think that is a characteristic now of our industry in that there are so many more decisions being made by insurers that affect many people, rather than individual physicians making those drug choice decisions.

Mr. SOUDER. Thank you.

Ms. JAGGAR. You're welcome.

Mr. SHAYS. I thank the gentleman. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Ms. Jaggar, if drug companies can promote off-label drugs, what incentive would they have to conduct or fund scientific research to ensure the drug efficacy for the new use?

Ms. JAGGAR. Mr. Towns, that really is the question, I think, which underlies the debate here and why the word "promote" is the key one under discussion.

The FDA's position, of course, is that it has a responsibility to assure the safety and efficacy of the drugs. When an application is submitted for a drug to be approved, it may be or it is likely to involve only one, or maybe in some instances, particular application of that drug, one particular reason for it to be approved.

If there are additional areas where the drug can be useful, what I think everyone would really like to have happen is, that the clinical testing be done so that we have confidence that the side effects or the negative effects from that additional use may not be detrimental to the individual.

When off-label drug use occurs, there has not been the approval process so that there is not the clinically proven circumstances that gives the user confidence. However, it doesn't mean that in many instances there haven't been studies that prove that there is value to that drug. This is why we suggest that the process of improving and making simpler and faster the approvals of these supplemental applications is a very important one.

Mr. SILBERMAN. If I might.

Mr. TOWNS. Go ahead.

Mr. SILBERMAN. There is no suggestion that promotion be allowed without any research. The suggestion is that promotion be allowed on the basis of research published in refereed journals or in compendia. The incentive remains to do that research; it's just a question of how much information needs to be gathered: enough to get into a refereed journal or enough to submit an efficacy supplement to FDA? The incentive is always going to be there to do something to gather information to serve as a basis for promotion.

Mr. TOWNS. Dr. DiMasi, I would like to hear your comments on that issue.

Mr. DIMASI. I think Mr. Silberman summed it up quite well. No one is certainly suggesting that off-label uses be used or reimbursed without sufficient scientific background and evidence. So,

indeed, there are incentives for someone to do that research, whether it be the manufacturer or private medical investigators, Government agencies, and so forth.

So there certainly will always be incentives to conduct research into new uses. The real question is; How much is acceptable?

Mr. TOWNS. You are saying that somebody should do it. What do you mean by that? I just want to make certain I understand you clearly. You didn't say FDA; you said somebody. Is there a reason for that somebody? I guess I'm listening maybe too closely.

Mr. DIMASI. Well, the research, clinical research, will be done not by the FDA but by the manufacturer or other parties—independent medical investigators, nonprofit institutions, Government agencies—who are interested in pursuing or investigating a particular use.

Mr. TOWNS. Right. So it leads me to this question: If there is less reliance on an FDA-approved label for supplemental use, wouldn't the credibility of the label be undermined by new drugs as well?

Mr. DIMASI. I don't think the credibility of the label would be undermined. There, obviously, would be some questions in the minds of some practitioners and patients about uses which are being used and reimbursed but have not found their way onto the product label.

Mr. TOWNS. If FDA approval become unnecessary for supplemental use, what criteria would we require or should we require? I just want to hold onto this a little while longer.

Mr. DIMASI. Well, I'm certainly not suggesting removing FDA's authority here in approving supplemental indications. But in terms of use in the marketplace and appropriate reimbursement, there certainly is the possibility of referring to organizations which can be set up by members of the compendia or professional societies to review in some sense what is out there in terms of off-label use and render opinions as to not what should be on the product label but what appears to be acceptable medical practice.

Mr. TOWNS. GAO, did you want to respond to that?

Ms. JAGGAR. Yes, sir. Mr. Towns, I think the desire is actually to have things go in the opposite direction: Not to remove FDA's role in approval for supplemental purposes, but to expedite that and make that more effective.

The FDA "Good Housekeeping Seal of Approval" is a very important one to consumers around the world, to patients and physicians, to purchasers, to insurers around the world because of what it says about the best information that can be gotten about the safety and efficacy of the drug that has been under consideration—for which the application is being submitted.

And yet what you don't want to do is put in place a situation or a system which denies further experimentation of and use of drugs for purposes other than the original one for which approval has been sought. And, I think the key is to make the process work better so you have the incentive for the pharmaceutical companies to do the research to get more uses on the label.

Mr. TOWNS. Thank you. Let me just sort of hold on for a minute longer. Dr. DiMasi, how current is your data?

Mr. DIMASI. Our last published study covered supplemental indication approvals through 1994.

Mr. TOWNS. Well, then do you agree with Ms. Jaggar's testimony that with the passage of legislation in 1993, third party reimbursement is no longer the problem it once was?

Mr. DIMASI. Third party reimbursement? I think that is still an issue in this country.

Mr. TOWNS. A big issue, small issue, medium-sized issue?

Mr. DIMASI. I think it's a fairly big issue. With the passage of the User Fee Act, though I think that the supplemental indication approval process has been improved.

Mr. TOWNS. Do you want to respond to that, Ms. Jaggar?

Mr. SILBERMAN. Our data were for cancer care and the 1993 legislation was specifically for reimbursement for cancer chemotherapy. That is where our expertise lies. And in terms of the diminution of the reimbursement question, it is specifically for cancer. We hear a lot less about those problems.

Reimbursement remains a constant problem and will probably grow as a problem as insurers try to figure out what treatments they will pay for and what treatments they won't pay for. It isn't necessarily revolving around the label. There is a question of reimbursement for autologous bone marrow transplantation. There is the question of reimbursement for length of hospital stay. There are dozens of issues that surface every day about what insurers will and won't pay for, but in the cancer area the label has ceased to be the limiting factor in terms of what insurers will or won't pay for, almost entirely because of the 1993 OBRA legislation.

Mr. TOWNS. Thank you very much, and I yield back.

Mr. SOUDER [presiding]. Thank you. Mrs. Morella.

Mrs. MORELLA. I was, first of all, curious about GAO's response to the suggestions that you made when Mr. Souder asked in the first question, Dr. DiMasi, because, again, they look like they make some sense, the paper SNDA's and submission by nonprofits. I don't know whether GAO has a comment on it. I am sure you have probably explored it in conjunction with your report.

Ms. JAGGAR. We are aware that the FDA has a number of activities underway to work on the SNDA approval process. There are draft guidance that they issued in December 1995. Comments have been received in the interim. And my understanding is that in a number of months they expect to finalize the guidance.

There have been improvements made in the process where they have, in fact, accelerated approvals for certain drugs to remove some of the bureaucratic barriers, if you will. This is an area that we think further action should be taken.

Mrs. MORELLA. And the submissions by nonprofits, is that something that is relevant, appropriate?

Mr. SILBERMAN. There were five suggestions made by Dr. DiMasi and they really mirror the issues that were discussed at length earlier this year in terms of reform of the entire NDA process, which is for the originals. Each has its attractions and each has its costs.

Third party review is really the question of in whose hands do we want to place the responsibility for reviewing applications and how much accountability should FDA have in that process. And those issues have been debated at length and are similar here to what they were for the original NDA's.

In terms of the interesting question about paper NDA's, I think paper NDA's become a much more feasible alternative the greater the difference between the benefits and the costs. In other words, as we move to supplemental indications where the benefit is enormous and the costs are minimal, then the standard of evidence in terms of paper NDA's becomes a much more reasonable alternative; that is, lifesaving drugs for indications where we currently don't have therapies where there is little cost associated with it, paper NDA is fine. But it is at the edges where it becomes more difficult.

In terms of the nonprofits, there is a cost of submission, and how do you motivate nonprofits to incur that cost? Especially, if it isn't a paper NDA, it is something more substantial than that. As you all know, the cost of submitting applications, original applications, is estimated at anywhere between $220 and $470 million. That is a significant amount relative to the profits.

Market exclusivity, we haven't explored the legal aspects of this and so I don't think we have a comment.

And, finally, the whole notion about some independent technology assessment function, either at IOM or through some other reputable body, gets back to the question of where we want to center this authority and the ability of organizations really structured to perform one role to take on additional responsibilities that are considerable.

Mrs. MORELLA. You also posed a question that I can see emanating from this, too. Is there an appropriate response that you would suggest from pharmaceutical manufacturers to extensive off-label use in those instances that have been cited—pediatric, rare disease, oncology indications?

Some patient groups are concerned that the prevalence of off-label use for pediatric, rare disease, and oncology indications serves as a disincentive to conduct clinical trials. I wondered, is there a responsibility? Does this tie into cost?

Ms. JAGGAR. I think clinical trials for pediatric uses are something that will be a thorny issue for us, perhaps forever, because the notion of doing clinical trials on children is a difficult one.

Mrs. MORELLA. It is rarely done, too.

Ms. JAGGAR. Yes; and that is why.

Mrs. MORELLA. Jim Moran has a bill that deals with that.

Ms. JAGGER. Yes; indeed. So it is a difficult issue and probably will not be one that is readily resolved. I think for rare diseases, the cost of doing clinical trials is something that, again, becomes an issue. You have pharmaceutical companies making substantial investments in developing new drugs because they expect to be able to make a return. They are for-profit companies. And so off-label use becomes more important in those instances. But that is why the notion of orphan drugs is an important one.

I think there will remain in pharmaceutical research and clinical trials some difficult issues when the cost is great, as it is for clinical trials, and the reward or the ethical sensitivity of it remains problematic.

Mrs. MORELLA. Is there an appropriate role of off-label promotion in pediatric, rare disease, and oncology treatment, if any of you want to address that?

Ms. JAGGAR. I think there is an appropriate role for off-label drugs, but the issue of promotion is, again, what a lot of this turns on. On what basis do you promote?

And, again, for pediatric diseases, you want as much confidence as you can that the drugs that you are going to be using are going to be effective and not dangerous for that particular population. The incentive is to have trials and to use other indicators—reputable studies or studies that are reported in refereed journals or other reputable sources as guidance for that, and go with that as decisionmaking assistance.

Mrs. MORELLA. One of the issues I see here from the GAO report has to do with reimbursement. About half the cancer physicians reported having been denied reimbursement for off-label treatment in the last 12 months, and then 23 percent reported that reimbursement problems influenced them to alter preferred treatments.

I would like to hear from you, Ms. Jaggar. And then you might want to comment on that, Dr. DiMasi, from your experience.

Ms. JAGGAR. Mrs. Morella, those results were from the study that we published in 1991 and the data were collected in 1989 and 1990, so they are, I think, old information. As we mentioned a little bit earlier, there was legislation enacted in 1993 that specifically went to coverage for cancer drugs, and reimbursement at this point for those particular drugs seems to be less an issue.

Mrs. MORELLA. Good.

Mr. SILBERMAN. There are other areas where off-label reimbursement remains a problem, and I think one of the ironies was pointed out by our finding where oncologists, as a way of circumventing the problems with reimbursement, were admitting their patients who didn't need hospitalization into a hospital simply because the actual drugs given in a hospital weren't examined by reimbursement. So you wind up paying more.

And we know that the same is true for other drugs. There is a published article in the New England Journal of Medicine documenting that for antidepressants. And so in an effort to save money, we may wind up actually spending more money because of shortsighted decisions.

Mrs. MORELLA. Did you want to comment on it, Dr. DiMasi?

Mr. DIMASI. No; really just to say that I concur.

Mrs. MORELLA. What do you do, research at Tufts? Tell us something about your background.

Mr. DIMASI. I am economist in a multidisciplinary research center at Tufts, called the Tufts Center for the Study of Drug Development. We are devoted to studying issues related to drug development and regulation and innovation and the economics of the pharmaceutical industry.

As I said, it is a multidisciplinary group. I am an economist. We have a pharmacologist, a molecular biologist, an attorney, and an M.D., Dr. Lasagna, is the director of the center.

Mr. SHAYS. Basically, it would be fair to say, Doctor, you are pretty much an observer of this process fulfilling, in some ways, the same kind of analytical role that the GAO has functioned in this. I mean, that is the reason why we invited you to be on this panel as opposed to the third one.

Mr. DIMASI. Yes.

Mr. SHAYS. Are you all set or do you have a few more questions?

Mrs. MORELLA. No, I'm all set. I think I interrupted you as you were commenting on reimbursement issues in general from what you found. I guess you would be looking at that too in the way of research, what you hear, what the studies are indicating.

Mr. DIMASI. I really don't have much to add to what the GAO representatives have said. I think that while reimbursement may have become less of a problem in the oncology area, it is still a problem in other areas. And while the label may not be as important in the oncology area, there are some related problems still associated with unlabeled uses in that area.

Mrs. MORELLA. And pharmaceutical companies, do you interact with them or do they contact you in terms of the question that I also asked regarding a role in promotion of off-label uses?

Mr. DIMASI. Well, you have used the word "promotion."

Mrs. MORELLA. As an economist, right?

Mr. DIMASI. Right. I do see a role for sort of loosening up restrictions on dissemination of information by manufacturers, although that would not move into the realm of what is traditionally called promotion.

Mr. SHAYS. Are you all set?

Mrs. MORELLA. All set. Thank you, Mr. Chairman.

Mr. SHAYS. Let me just say I feel like we are beginning to speak softer and softer and softer. I would like to get a little life in here. This is a very serious issue.

The bottom line is, as I see it, and then I want you to respond. The bottom line, as I see it, is this: You have drug companies that basically have a drug tested at tremendous expense, and then once it is on the market they and others find other uses for it. The question is: Is there an incentive for them to find the least expensive way to become a licensed drug? And then is there an incentive for them to market and how would they do that, I would like to know, the drug for other uses?

And, to me, what boggles my mind when I think about it, is we test the drug and they have to go through extensive testing to see that not only is the drug safe but it has efficacy, and then all the secondary uses we have no testing that says that there is any efficacy to it. And we don't also know if it is safe. We don't know at what levels it is safe and not safe.

I am wondering if this isn't just a big back door to enter into the market. This is not a criticism of FDA. I mean, this committee has not used either HCFA or FDA to be the whipping post. But is there, because of the process, just a real incentive to find the easiest way to get on the market and then find all these other ways to market the product to other people?

I mean, we have experts. You are all experts and we are really getting into the general view of it, so we are not testing your analytical minds as much as I would like. But the bottom line is I would like you to respond. First, my request is that you respond to what I have just said. Put that into some perspective. I am going to ask all three of you. Dr. Silberman, I am going to ask you to respond as well.

Ms. Jaggar.

Ms. JAGGAR. Mr. Shays, again, the issue is promotion, exactly as you have framed it. What is key here is that when FDA approves a drug, then the pharmaceutical company can promote it when it is on-label. When something is off-label, there are substantial and extensive restrictions and constraints on that promotion process.

Mr. SHAYS. But it is just limited to promotion; it is not limited to use.

Ms. JAGGAR. True.

Mr. SHAYS. I mean, reimbursement is a factor as well.

Ms. JAGGAR. True. You don't want to limit use because the practice of medicine, as you know, is both science and art and involves individuals and physicians looking at new ways to use drugs—sometimes in combination, sometimes for purposes not used before—to see if they work.

Mr. SHAYS. But isn't that a double standard? And I'm going to get to all of you. Isn't that an incredible double standard? We have one test to get in the market and then—and you don't use that same argument to get in the market. You don't say, well, a doctor is just deciding if they want to use it. They have to have that drug licensed. The sellers have to have it licensed before they can put it in the marketplace. And so you are using two different standards.

Ms. JAGGAR. I can see how it could look like a double standard, and yet, if you look at the practicalities of what really is possible in terms of clinical research and in terms of medicine and the contributions that are made, the role of the FDA and the role of pharmaceutical companies, if you were to put in place a standard that required that kind of clinical research for every single use, you would really constrain the availability of drugs.

Mr. SHAYS. I am not suggesting that. I am just suggesting it is an amazing double standard. And if the argument applies to the secondary uses, in your argument why doesn't it apply to primary uses? I'm sorry. Why don't you finish.

Ms. JAGGAR. I would just say that one of the reasons that this is of concern and that FDA is dealing with it very carefully is, they don't want to remove the incentive that the clinical trials be done. In other words, when something is promoted, it is much more likely to be used. It is widely known that the market increases. That is definitely a driver.

So if, in order to promote, approval is required, that is an incentive for pharmaceutical companies to seek that approval. And FDA's job is to make the process be expeditious, as cost-effective as possible, so that we have accurate information and complete information.

Mr. SHAYS. Are you talking about primary use or secondary use?

Ms. JAGGAR. Secondary use, all uses.

Mr. SHAYS. Even primary?

Ms. JAGGAR. Right.

Mr. SHAYS. Dr. Silberman.

Mr. SILBERMAN. If I could divide this into four issues; first of all, the label, the use of the drug, the information available about the drug, and then promotion of the drug. And I think that there is an intersection of all those, and if I could just try and disaggregate those.

The standards for what goes on the label, to the best of our understanding, are consistent for primary and secondary indications; that is, you have to demonstrate to FDA's satisfaction that the drug has substantial safety and effectiveness for the condition it is supposed to have.

Mr. SHAYS. Only for the primary use.

Mr. SILBERMAN. For the secondary as well, you have to demonstrate. So that if a drug is approved as an antihypertensive in an elderly population and then you want to show that it has efficacy in a younger population, you have to convince FDA through your research that is of the same standard as the original.

Mr. SHAYS. Who is they? The drug company?

Mr. SILBERMAN. The drug company has to convince.

Mr. SHAYS. What is to prevent a doctor from prescribing that drug for a use unrelated to the label?

Mr. SILBERMAN. That is use. That is the second question.

Mr. SHAYS. OK.

Mr. SILBERMAN. So the first issue is the label. The standards of evidence to get on the label are supposedly consistent for all uses.

Mr. SHAYS. Being new at this, I am just going to clarify one thing so I don't lose it. I made an assumption that the label could only be focused on primary use. You are making the point to me that once they have primary use, they can make a claim on the label for secondary use and begin to back it up. They haven't yet had to document it.

Mr. SILBERMAN. The label is changed by the Food and Drug Administration, and the way that is done is that you submit evidence for a supplemental application.

Mr. SHAYS. OK, you answered the question.

Mr. SILBERMAN. So the label is for whatever evidence you submit originally. And then if you want to change it, you have to submit more evidence. The FDA reviews that, and that is the data that Dr. DiMasi and we presented on how long that review takes.

In terms of use, I think it was very wisely determined that physicians should have considerable discretion in what they prescribe for patients. Now, they can only prescribe—that is actually a little bit of an overstatement—they can mostly prescribe drugs that have already been approved for at least one indication. There is, in fact, the ability in recent years to provide drugs to patients that have not yet been approved, through a compassionate IND.

Mr. SHAYS. Being a skeptic here, particularly since I see so much of it in cancer use where people are really desperate, I have to believe that if a doctor feels that this drug has some efficacy without it being labeled, that they will prescribe it and a patient will willingly use it.

Mr. SILBERMAN. And that is what our results show; that that, in fact, was occurring.

Mr. SHAYS. OK. And so I am having a hard time reconciling your previous statement which was, in essence, that there had to be shown a secondary use.

Mr. SILBERMAN. That is for the label.

Mr. SHAYS. Right; OK.

Mr. SILBERMAN. And in order to change the label. The use isn't completely consistent with the label. We know that to be the fact through our data.

Mr. SHAYS. And to what extent is it not reflective of all the use of the drug? Some of these statistics boggle my mind.

Mr. SILBERMAN. What we showed was that more than half of the cancer patients that we looked at were receiving at least one of their drugs off-label.

Mr. SHAYS. Yes. So it was off-label; it clearly wasn't a primary use. It wasn't the original approval for that drug.

Mr. SILBERMAN. Right. That drug was typically approved for some other form of cancer and was now being used for this form of cancer.

Mr. SHAYS. So the bottom line is it is being used for something that is not even on-label.

Mr. SILBERMAN. Right.

Mr. SHAYS. I don't know quite what the end result is of it, but that, to me, is a significant fact.

Mr. SILBERMAN. It says that the label will never, under the most ideal circumstances, be able to keep up to date with the latest in research. If you are a physician and I am your patient and an article appears today that says that this drug might work against a condition that I have that is necessarily fatal, I want you to give me that drug.

Mr. SHAYS. I will tell you that if there is even the hint of a possibility that it might be helpful, for someone who thinks they are going to die with no hope in the world, they are going to contact their doctor. The doctor is going to potentially prescribe it, maybe not, and it is going to be used. And I understand. It is not a criticism. I am just trying to understand the difference.

Mr. SILBERMAN. And there is no prohibition against that use.

Mr. SHAYS. OK. Why don't we get to the information and promotion, then we will get to you, Dr. DiMasi.

Mr. SILBERMAN. I will switch them around. I'll talk about promotion for a second.

Mr. SHAYS. OK.

Mr. SILBERMAN. In this environment, as Ms. Jaggar mentioned, where pharmaceutical firms are really, for the first time, facing enormous competition, the viability of the industry is, to some extent, at stake, and their ability to demonstrate the true utility of their products. So, understandably, if they have some new use that they think is worthwhile, they want to tell the world about it and they want everybody to know about it. They want to be able to promote it.

Mr. SHAYS. Right.

Mr. SILBERMAN. On the other hand, the Food and Drug Administration argues, legitimately, that in their responsibility through FD&C to regulate promotion, they want to restrict promotion to what they have already approved, to what FDA has already approved. And there is that dilemma. Do we allow use?

Mr. SHAYS. How is the dilemma resolved? By the way, to the other committee members, we will do a second round, if you will, because I would like to pursue this a little bit more so I am just taking a little longer.

So what is the bottom line to it?

Mr. SILBERMAN. The bottom line is that we need some policy that, on the one hand——

Mr. SHAYS. OK, so that is one answer. I'm sorry I interrupted you. I'll let you finish your statement and then I will interrupt here.

Mr. SILBERMAN. We want physicians to know as much as they can about every possible use of the drugs.

Mr. SHAYS. So it is an unresolved issue of gigantic proportions.

Mr. SILBERMAN. Yes.

Mr. SHAYS. The question is: Do we allow them to promote a drug that is not the primary use but is on-label and we allow them to promote any part that is labeled? Is that correct?

Mr. SILBERMAN. Do we allow pharmaceutical firms to promote on the basis of research that is of a certain quality and stature.

Mr. SHAYS. No. I want to know, if it is on-label, are they allowed to promote it?

Mr. SILBERMAN. Yes.

Mr. SHAYS. If it is not on-label, are they allowed to promote it?

Mr. SILBERMAN. No.

Mr. SHAYS. OK. And then the issue is?

Mr. SILBERMAN. Should we allow them to promote it on that basis?

Mr. SHAYS. Well, I think I know my answer. Dr. DiMasi, anything of the comments I made and observations? I'm just trying to get some bottom line senses of where the real battle lines are.

I mean, for all of you this is old hat. For us, it's not, but we bring a fresh look to this and we also may bring some impetus to resolve it because I have a feeling that this is the kind of issue that will never get resolved unless someone pushes it. And yet I can see some really gigantic potential problems if we don't.

Mr. DIMASI. OK. I believe that it is important to have high standards for efficacy and safety for product labels and there is a benefit to establishing that—establishing an initial indication and establishing that a drug is safe and effective.

That tells you a good deal about the drug, usually, in potential secondary uses. You know a good deal about the safety of the drug in many cases, although the standards, as Mr. Silberman said, are the same for supplemental indications as they are for original indications.

Mr. SHAYS. Just to make sure I'm hearing you, are you saying that if a drug gets in the market we have achieved one basic threshold that that's safe and that the off-label issue is really whether there is efficacy, or is there even still a safety question on off-label?

Mr. DIMASI. There are some safety questions.

Mr. SHAYS. But just so you know what is in my mind here, I mean, a physician always has the right to prescribe any drug for any disease, whether or not the disease indication is on the label. We know that. And I am not suggesting a change there.

But what is interesting is if a drug hasn't been labeled at all and it's not on the market, that physician doesn't have a right to use that drug. And so it is like we have one standard for how you get

in the marketplace, but once you get in the marketplace there is a whole different standard.

And so I am making this assumption, as a generalist who is not a doctor, that we must have come to the conclusion that, boy, we are really going to make it hard to get on the market because once you get on the market, who knows how that drug is going to be used. But once you are on the market, we have made a sense that, you know, we have tested it on every conceivable animal, person, and so on, so we know it is not going to kill him, but we can't guarantee that there is efficacy involved, that it will be effective in an off-label use. That is where my mindset is.

Mr. DIMASI. I think what is most important is that physicians have the best and most up-to-date information available to them. There are a number of ways we can work toward that goal. One is to attempt to speed up the approval process and provide guidelines for firms in submitting supplemental applications so that they can perhaps develop those new uses more quickly and less expensively and submit applications that are in good order and will be approved.

Second, though, I think a lot can be done in the area of education. And that can perhaps involve a lot of the professional societies, as I have mentioned earlier, such as the Institute of Medicine and other organizations, to assist in getting information to physicians, practicing physicians, as quickly as possible on just what the current state of knowledge is about the use of already approved drugs for a variety of indications.

Mr. SHAYS. I am going to call on Mr. Souder if he wants to respond in just 1 second, but I gather I am making an assumption that, somehow, if you can't promote the drug, that is a negative for the drug company.

But in this day and age, particularly as it relates to serious illness, I have a number of dear, precious constituents who have life-threatening diseases that are on the Internet and they are communicating with a wide host of people. And it is almost like you could subtly suggest this could be used and then people are going to use that drug. And there is a lot of experimentation and you have patients who know more than some doctors, it seems, because they have devoted their lives to trying to cure themselves.

And so what is in the back of my mind is that, in one sense, it is a positive for a pharmaceutical company if they can just get on the marketplace as cheaply and quickly as possible, then it is a positive that they can expand its use. And I have a sense that is happening.

And it is a negative, however, that they can't promote it, but I am not as impressed with that negative because there are a whole host of ways to promote it without really, you know, advertising it on TV.

And I am just stuck with then the only other negative is the reimbursement issue. If you can find ways to be reimbursed for the drug without it being, you know, going to the hospital and gaming the system. I mean, there are a lot of reasons why we want to resolve this. We want people to have knowledge so they use it well. We don't want to game the system. We don't want people to spend more when they shouldn't.

But I have a feeling that nobody is really suggesting a solution, like we are all kind of wrestling because we don't have a solution. And maybe, it is like let sleeping dogs lie. Someday we may find that we regret that we haven't come to grips with this. I mean, that is my take on what I am hearing as I heard Mr. Souder ask questions, and Mrs. Morella.

Mr. Souder.

Mr. SOUDER. I wanted to try to figure out a little bit of a scale question and I am trying to figure out how best to do this. I thought it was very interesting, Dr. Silberman, your earlier response on the paper SNDA's that the potential benefit, if it is great and the cost is low, that is not a big deal because we would take those risks.

Obviously, the key thing here is that from a patient perspective, if I was in that situation I would want the best concerned. If I am a doctor, I don't want any hands tied. As an employer, I have concern about my insurance. If I was an insurance company, I would be concerned about it. And if we are the Government and we are paying a lot of this through Medicare and Medicaid, we have a concern. And as taxpayers, we have a concern.

So part of this is a question of scale. Let me ask first off, and this may be more to Dr. DiMasi as an economist, when somebody makes a movie, they estimate as a firm how much they are going to get the first run, second run, foreign, videotape, television rights, and the cost.

Do companies, depending on the drug—I realize it would be a wide variation—but do they have built into their costs a factor that there is going to be a secondary usage and what percentage of the drug market do they think is a secondary usage? I mean, that could cover a wide range of drugs but, nevertheless, you have bad debt allowances can vary a lot too. Any kind of expense category.

I mean, are we talking about something that is 2 percent of their business overall, a half a percent, or is it 20 or 30 percent? And if it is 30 percent for some drug categories, what kind of dollar scale are we talking about?

Mr. DIMASI. Well, I don't know what the dollar figures are. I think it varies substantially from drug to drug. In some cases, the firms will know as they are developing the initial indication that there is another indication or several other indications that look very promising. In many other cases, new uses are not discovered, if you will, until many years after initial approval and those new uses will not have been factored into their thinking and their planning.

Mr. SOUDER. So it would just be like a bonus profit?

Mr. DIMASI. Yes, yes, exactly.

Mr. SOUDER. It must not be that regular or that big or companies would have to have some sort of an accounting method; otherwise, it would screw up long-term planning. You wouldn't have value stock markets. There has got to be some predictability that you expect if you are Eli-Lilly, to use an Indiana example, that you are going to hit something like that. Or if you have a series of experimental drugs in the AIDS area or you are testing, it is not likely that just all of a sudden there is a big hit.

Mr. DIMASI. True. And if you are a large enough company, if you have a large enough portfolio of drugs in development, you can perhaps be reasonably good in terms of predicting what you are going to get from new indications.

It also depends a lot on what area you are working in. Our data indicate that approved new uses tend to be concentrated in certain therapeutic categories, relative to the way that original uses are distributed. In particular, there are lots of approved new indications.

Mr. SOUDER. But I'm trying to get back to my question. You are trying to explain the complexity, and that is difficult to do in the limited timeframe we have here. But I think we are impressed that it is complex, but we don't have a feel for the scale here. Dollar-wise, I mean, are most of these things medicines that cost $2 and they are prescribing them here and there, or are we talking something that is potentially a significant percentage of all the drug market? And that, indeed, as we discover new things, let me try my second question. Do either of you have a comment on the first part?

Mr. SILBERMAN. I think we actually have some data on that.

Mr. SOUDER. OK, I'd like that.

Mr. SHAYS. If the gentleman will yield, what we are really, I think, trying to get—and correct me if I am wrong—is there a percent of off-label use that comprises the market? I'm sure we can get it from someone. And, if so, what is that? And is this unique to some drugs or many drugs? Do most drugs that come on the market end up having off-label use, or is it just some and then those some have significant use?

Is that what you're getting at?

Mr. SOUDER. Yes.

Mr. SILBERMAN. The only two studies that I am familiar with that put precise estimates on it are the study we did in cancer and then another study that was published this year in AIDS. I think that in the rare diseases area and the pediatric area there is such widespread acknowledgment of the prevalence of this that no one is going to bother to actually do the study because whether it is 85 percent or 89 percent, we know it's very high.

Now, in the cancer area——

Mr. SOUDER. And pediatrics as well?

Mr. SILBERMAN. Pediatrics as well. I mean, everybody knows that lots of drugs are not labeled for children that are given to children for diseases that occur in children, like asthma. You know, fairly common pediatric illnesses.

In the cancer area, we are, I guess, cursed with the strange reality that the most prevalent diseases are the ones that are least susceptible to chemotherapy and the ones that take the longest time to kill you. So we're talking about the solid tumors—breast cancer, lung cancer. There are the hematological disorders, diseases of the blood, lymphoma and leukemia, that are very quick and respond to chemotherapy.

Now, if I am going to do a clinical trial to demonstrate that my drug has some efficacy against a cancer, I want to do it in a population where I know the answer quickly. You know, if you don't have a response in a leukemia patient, that patient dies quickly.

If you don't have a response in a colon cancer patient, that patient could still live for 15 years. So there is a natural incentive to test your drugs against hematological disorders and chemotherapy works better against those.

But the real market is in the solid tumors. You don't have 6,000 patients; you have 60,000 patients. Just in terms of dollar figures, of the most widely used drugs that we found, carboplatin was used off-label frequently. The cost per patient was $5,500 in 1990 dollars in terms of one regimen of this, six cycles. Our cost ranged from a low of a few hundred dollars to a high of about $10,000 per patient, though a lot of the money is being used off-label.

What we found, and this should come as no surprise, is that reimbursement denials were not for all off-label uses but for the off-label uses that were expensive.

Mr. SOUDER. Can I ask one other variation of the same question? In trying to gauge what impact this has, in particular on the Government, if the ones that are denied are often the most expensive, I would assume that particularly for anything that really pushes past $5,500 a year, you start to get into the phenomena that we see with Ricky Ray and others where, in effect, you can push families into financial a situation where they go into Medicaid and Medicare.

Do you have any what kind of Government reimbursement costs we have in these areas and what percentage, and do you expect this to grow? In other words, as we come up with more miracle-type drugs that deal with really devastating diseases and everybody wants access to those, isn't this a potential large growth element of our Medicaid and Medicare budget?

Mr. SILBERMAN. The specific answer for cancer is that we allowed reimbursement for other issues, so the off-label has disappeared for that. But the general statement is exactly on the mark: every day we can do more and more for more and more patients and we can't pay for everything, so the decision about what we reimburse is critical. That is, I think, the central dilemma of health care: what we are going to pay for and what we are not. So you're right on the mark.

Mr. SOUDER. And that partly requires us to know costs.

Mr. SILBERMAN. And how well things work.

Mr. SOUDER. And what the costs are.

Ms. JAGGAR. Mr. Souder, perhaps I would bring to your mind an article I know you've seen recently in the paper about the high cost of the new AIDS drugs. So many people are aware that they offer great hope, new hope for extended life or even better than that; however, the cost is extremely high.

Many AIDS patients achieve their coverage through Medicaid and so there are State programs that are in the process of making some very difficult decisions. Can they add additional money to pay for these expensive drugs? Do they have to ration the coverage in some way? Can they not cover the new expensive drugs and only continue to cover the old drugs that were less expensive?

I think that is an example of a very real dilemma that many States are facing right now. And, of course, Medicaid is partially funded by the Federal Government, so it has Federal implications.

Mr. SOUDER. And it presents a real tough process. Having talked to different individuals in the pharmaceutical field, if it costs $220 to $450 million to get a clearance, of course that is going to be an expensive drug, given the number of cases, which is why you get the off-label and we go right back into the cycle.

But thank you.

Mr. SHAYS. Mrs. Morella.

Mrs. MORELLA. I know we've got several other panels that are going to be shedding light on some of the questions that we posed, and I think this panel has been excellent.

I wonder as a final shot, do you recommend that there should be any furtherance of studies that FDA should be responsible for thinking in terms of pediatric work, more that we need to know? Is there an extended role in discerning needs and application, because of studies and collaboration, partnerships, that you can see for FDA?

Ms. JAGGAR. If I might respectfully urge you to inquire of FDA and also the individuals from the American Academy of Pediatrics who will be speaking later. I know that FDA is very aware of and concerned about this issue and looking for ways to better discern from the information that comes from clinical trials on adults, for example, what the possible implications would be for pediatric cases. I don't think there is a simple answer to it.

Do you have anything to add?

Mr. SILBERMAN. I was hoping she wasn't going to look at me. No, really, nothing to add on that.

Mrs. MORELLA. Dr. DiMasi.

Mr. DIMASI. Nothing to add either.

Mrs. MORELLA. Nobody wants to touch it. OK, Mr. Chairman, I yield back.

Mr. SHAYS. Dr. Silberman, in my statement we basically, I think, took from your work. We said for 50 million children, 40 million cancer patients and 20 million Americans suffering from rare or orphan diseases, most of their treatments are off-label.

Is that correct?

Mr. SILBERMAN. From our work on cancer, we know the exact amount. From the information we have gotten from the various groups representing those other patient populations, there is such widespread acknowledgment of the prevalence of this use that I feel fairly certain that it is correct.

Mr. SHAYS. Are you comfortable with what I just read then?

Mr. SILBERMAN. That there is widespread use?

Mr. SHAYS. I said, "For 50 million children, 40 million cancer patients and 20 million Americans." Some of them could be all the same.

Mr. SILBERMAN. For cancer patients it is a little tricky because some cancer patients are not candidates for chemotherapy and I don't have a precise estimate of the number.

Mr. SHAYS. In 1991, the General Accounting Office—that was your study—found off-label use of cancer drugs widespread—that's true—encompassing a third of all drug dosages to those patients. True? More than half the cancer patients that GAO surveyed received at least one off-label drug?

Mr. SILBERMAN. That's true.

Mr. SHAYS. OK. And as we will hear from our witnesses today, we said pediatric labeling is also scarce, with up to 80 percent of drugs administered to children prescribed for off-label or unapproved indications. True?

Mr. SILBERMAN. That was what we were told.

Mr. SHAYS. It is estimated that 90 percent of all rare disease treatments are off-label.

Mr. SILBERMAN. The actual estimate was that we were given the number of drugs that were approved through the orphan drug provision and the number of rare diseases, and just from those two numbers you can see that there must be an enormous amount.

Mr. SHAYS. I mean, this is an enormous issue. I am just going to ask you two questions that really are submitted for us when we start to begin to do our report, and I just need to make sure this is on the record.

I am going to ask you, Dr. Silberman, how does the lack of efficacy and dosage information on products for which there is extensive off-label use affect the quality of care for pediatric, cancer, and rare disease patients? That is kind of a big answer so I am asking you to do something I don't ordinarily do; I am asking for not a 10-minute response.

So how does the lack of efficacy and dosage information on products for which there is extensive off-label use affect the quality of care for pediatric, cancer and rare disease patients?

Mr. SILBERMAN. I think that is the central question and we don't have an answer to that.

Mr. SHAYS. OK. Are we going to allow that one to stand or should I pursue that a little bit? We'll have to ask other witnesses.

And what changes in the supplemental new drug application review process would you recommend to facilitate more complete and timely labeling of drugs?

Mr. SILBERMAN. I think the data that Dr. DiMasi presented clearly show a process that took a long time, and perhaps an inordinately long time. And yet the easiest thing we can do, the quickest thing we can do, is just try and make it faster. Now, the data we presented show that we may, in fact, be achieving that. That is the FDA side.

Incentives for companies to submit applications need to be examined and the standard of evidence required needs to be examined. But if we can make this process work better, it is in everybody's interest: reimbursers, FDA, the public, physicians.

Mr. SHAYS. You all have been very interesting and I appreciate your patience with at least my learning knowledge of this issue. So we will go to the next panel unless there is anything any of the three of you want to say as a closing comment.

You have been very interesting, very helpful, and I am sure we will have you back. Thank you very much.

We do have a vote, but I think what I would like to do is just go then and vote. We are going to go vote and probably by the time we are done it is going to take us 15 minutes, but we are going to try to hustle back here for our next witnesses. Sorry to hold you up. This committee is recessed for approximately 15 minutes.

[Recess.]

Mr. SHAYS. The hearing is resumed. We call on Dr. Friedman, who is the Deputy Commissioner for Operations, Food and Drug Administration, accompanied by William Schultz. And are you also accompanied by Janet Woodcock?

Dr. FRIEDMAN. Yes, sir; and she should be here. She was just outside the door.

Mr. SHAYS. Thank you. I am going to wait to swear all of you in at the same time. I appreciate you being here.

Dr. FRIEDMAN. Our pleasure.

Mr. SHAYS. Thank you. Welcome. If you would all raise your hands.

Dr. FRIEDMAN. Sir, there are other people accompanying me that, should questions be asked that they can answer, would you like them to be sworn as well?

Mr. SHAYS. Yes; and if they don't mind standing up. And we would identify you. It is very nice of you to do that now. Could the both of you identify yourselves?

Dr. HAFFNER. Marlene Haffner. I am director of the Office of Orphan Products Development.

Mr. SHAYS. It is nice to have you here.

Dr. LUMPKIN. I am Murray Lumpkin. I am the deputy center director at the Center for Drug Evaluation and Research.

Mr. SHAYS. Thank you very much.

Mr. RAY. And my name is Seth Ray. I am with the general counsel's office.

Mr. SHAYS. If you all have cards to give to our recorder, that would be helpful to her, I think. Correct?

COURT REPORTER. Yes; thank you.

Mr. SHAYS. OK. Now, when you said, "Yes, thank you," are you also recording yourself now? Are we going to see you in this transcript?

COURT REPORTER. I can take it out.

Mr. SHAYS. Oh, no; you can stay on. If you would raise your right hands, please.

[Witnesses sworn.]

Mr. SHAYS. And I would like to note for the record that Dr. Friedman did a yeoman's job in trying to raise his injured right arm. Thank you. I would have been a little more thoughtful of you had I thought about it first.

My sense is that, Dr. Friedman, you are going to be giving testimony and you are accompanied by William Schultz and Janet Woodcock. And then there are other members who might respond to a question, and we welcome that as well.

Dr. FRIEDMAN. That is correct, sir.

Mr. SHAYS. Let me just say that we welcome your testimony, however long, however you feel you need to get your story out. We welcome you here.

Dr. FRIEDMAN. Thank you very much, Mr. Chairman.

Mr. SHAYS. I'm sorry to interrupt just before you start. Given that you have already heard questioning and dialog, anything you want to interject about what you have heard, comments and so on, feel free to amend your statement or whatever based on that. I welcome you responding to questions you have already heard before we ask the second time, if you feel it is appropriate.

STATEMENTS OF MICHAEL FRIEDMAN, DEPUTY COMMISSIONER FOR OPERATIONS, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY WILLIAM SCHULTZ, DEPUTY COMMISSIONER FOR POLICY; DR. JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH; MARLENE HAFFNER, DIRECTOR OF THE OFFICE OF ORPHAN PRODUCTS DEVELOPMENT; MURRAY LUMPKIN, DEPUTY CENTER DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH; AND SETH RAY, GENERAL COUNSEL'S OFFICE

Dr. FRIEDMAN. Thank you very much, sir. We will try and do that. Let me recap, if I may, some of the important issues that were previously mentioned.

The fundamental precept of drug regulation in this country is that products be proven safe and effective before they can be marketed. The requirement that products be proven effective on the basis of proper clinical studies was first adopted by the Congress in 1962. In adding the concept of effectiveness to the Food, Drug and Cosmetic Act, Congress specifically intended that this requirement would apply not only to the initial indication for a drug, but also to indications that come to light after that initial new drug application has been approved.

The history of the Food, Drug and Cosmetic Act indicates that Congress did not intend FDA to interfere with the practice of medicine, and this is an issue that you were discussing just previously. Thus, once a product is approved for marketing for a specific use, FDA generally does not regulate how and for what purposes physicians prescribe that product.

A licensed physician can prescribe a drug for other uses in treatments, regimens, or patient populations that are not listed in the FDA approved labeling, in keeping with appropriate standards of medical practice. And these are the uses that are referred to as off-label or unapproved or unlabeled or extra-labeled uses.

It is important to point out that there are two general situations in which off-label use occurs, and you outlined those just previously. First, there is the situation in which strong scientific data exist that support the off-label use and; second, there is the situation in which an off-label use exists but without sufficient supporting scientific data.

The FDA has an interest and ability to work with industry and consumer groups to address the first situation where data exist. We can clarify and simplify our processes so that industry will be encouraged to submit the supportive data for an off-label use and, thus, make it an on-label use.

The second situation where inadequate data, scientific data, to support an off-label use exist is a more difficult one. It is not a situation that can be addressed specifically by FDA alone. All the involved parties—and some of these constituencies have been described before—need to work together to identify incentives so that industry and academia, patient groups and public groups and the reimbursement industry, can work together to conduct the studies necessary to know if an off-label use is effective and if it is appropriately safe and, therefore, should become part of the product label.

There are many off-label uses of approved drugs and there are already many good reasons for drug companies to submit efficacy supplements. One of these is the physician, via the approved labeling, is given more complete information about the drug's use, proper dosage, and other important information. And, ultimately, of course, it is that physician's patients who benefit from that information.

Second, as has been pointed out, manufacturers can promote the use of that product. Third, approval is often considered by third party payers, the reimbursement industry, in making a reimbursement decision for drugs or products.

Fourth, a sponsor's ability to get its drug included in an HMO's drug formulary or other sort of managed practice formulary can be significantly enhanced. And as was pointed out previously, this is an enormous and growing economic incentive for the pharmaceutical industry.

And another point to be mentioned is that drug companies can present the FDA findings to drug approval bodies in other countries and, thus, perhaps enhance their ability to gain approval and perhaps reimbursement for use in other markets.

Now, so far today you have heard that there have been meaningful improvements in the efficiency in which the agency processes its supplemental applications. Data has been presented to you, and I can present more, should you like.

While we are gratified with this trend, we are not satisfied. The FDA is undertaking initiatives to encourage and expedite still further efficacy supplements for these unapproved uses. We are doing a number of things and have several plans for additional progress in this area. Our goal is to have the product's label more completely and more accurately reflect clinical usage that is safe and effective.

There are many constituencies interested in this issue. You will hear from some of them today. And all these constituencies will benefit from this overall effort.

Now, earlier this year, the Food and Drug Administration assembled an internal working group to examine in some depth the range of issues that influence whether a supplemental indication makes it onto a product's label. This supplemental indications working group is focused on identifying barriers to sponsor submission, some of the very same questions that you raised this morning, Mr. Chairman, of these supplemental indications, and to try and identify means to lower or eliminate disincentives or barriers.

The group is considering a variety of strategies to encourage the submission of supplemental applications and developing a clear articulation of the scientific standards, level of evidence, and so forth, used by the agency in assessing the safety and effectiveness of a new indication for that product.

To address the problem of unlabeled uses effectively, FDA must adopt a much more active role in identifying important supplemental indications, facilitating their study and evaluation and, if effective, incorporating these uses onto the label. The best solution to the problem will be achieved by getting as many of the affected constituents as possible involved in creating strategies that will get new uses onto the label.

It is also apparent that for products that lack marketing exclusivity and for supplemental indications that may benefit only a small population of patients, new and creative strategies are needed to reliably induce commercial sponsors or other sponsors to pursue these indications.

To get these uses onto the label likely will require the allocation of public funds, particularly where additional research data would have to be developed to demonstrate that a use is safe and effective.

Current proposals under discussion within our agency envision that we will provide, first of all, much more clear, consistent, and simple standards to be applied in making decisions concerning supplemental safety and effectiveness reviews; second, to become more accessible and responsive to the broad array of constituents who have an interest in whether or not a use is on the label; and, third, to more actively identify unlabeled uses preliminarily assessing the data that support that use and actively encouraging commercial sponsors and other interested parties to participate in pursuing the approval of these uses.

Our obligation to the public is to help assure that physicians and other health care practitioners have the best information available. Patients deserve this information; physicians require this information.

The supplemental applications and review process can help ensure that the information generated by medical research is accurate and, in fact, does represent a safe and effective new use that the public can benefit from. The labeling of a drug for a new use assures that there is strong and reliable scientific information upon which to base the use of the product and that that information is widely available, as widely available as possible. With such information on the label, we can give practitioners the information they need to offer the best possible therapy to their patients.

We are committed to working with you, with industry, with patients, with physician groups, with research organizations, and a variety of other constituencies, to assure that the best possible information is available as widely as possible. We are very seriously committed to this important opportunity, as we see it.

I would be very happy, all of us would be happy, to answer any questions you might have, Mr. Chairman.

[The prepared statement of Dr. Friedman follows:]

INTRODUCTION

Mr. Chairman and Members of the Committee. My name is Dr. Michael Friedman. I am the Deputy Commissioner for Operations at the Food and Drug Administration (FDA or "the Agency"). With me today is Mr. William Schultz, Deputy Commissioner for Policy, and Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER).

I appreciate the opportunity to testify on the important issue of supplemental indications for approved prescription drugs. FDA supports and encourages the labeling of new indications for approved drugs. We have been working actively to encourage the industry's submissions of efficacy supplements and to ensure that such supplements are reviewed in as timely a manner as possible.

THE NDA PROCESS

Let me start with a brief discussion of the process for approving new drugs in the United States. When a sponsor has completed and evaluated its initial research on a drug, including animal research, and has determined that a drug appears to be a promising treatment for a medical condition, the sponsor then proceeds to study the drug in humans. At that time, the sponsor submits to FDA an Investigational New Drug Application (IND). An IND includes protocols for studying and collecting data on the safety and effectiveness of a drug in humans. The initial clinical studies of a new drug often only include studies for one or a discrete few uses of the product. FDA reviews the IND to help ensure that: (1) the product is reasonably safe to be

tested in humans; (2) there are adequate protections of the human subjects, including informed consent; and (3) the clinical trials are adequately designed to permit an evaluation of the drug's safety and effectiveness.

In order to market a drug in the United States, it must be the subject of an approved New Drug Application (NDA). Once the IND clinical trials are completed and the data developed, if the sponsor believes the data support the safety and effectiveness of the drug, the sponsor submits an NDA. An NDA includes all data on the safety and effectiveness of the drug for a particular indication. The data include detailed results of clinical studies, information on how the drug is made and how quality is maintained, and the results of animal studies. FDA also requires samples of the drug and its proposed labeling. The reports of a drug's clinical studies are provided in detail so that FDA can evaluate the data. The data from controlled clinical trials are especially important because they provide the only basis, under law, for demonstrating effectiveness. They answer the question, "Does this drug work for the proposed use ?" The information derived from the clinical trials also is used to determine any adverse effects.

At times, FDA asks for advice from outside experts on a particular drug application. These experts are members of FDA's drug advisory committees and have specialized experience involving the drugs under the purview of the specific committee. These expert advisers add to FDA's understanding, so that final Agency decisions more likely will reflect a balanced evaluation.

In the final analysis, FDA's decision whether to approve a new drug for marketing boils down to two questions:

- Do the results of adequate and well-controlled studies provide substantial evidence of effectiveness?
- Do the results show the product is safe under the conditions of use in the proposed labeling? Safe, in this context, means that the benefits of the drug appear to outweigh its risks, and that those risks are predictable.

Once a drug is approved for marketing, a sponsor (or manufacturer) may promote the use of that drug for the approved indication or indications. This promotion can be to health care practitioners, health maintenance organizations, health insurance plans, and directly to consumers. After the initial approval, if a sponsor wants to change how its drug is manufactured or the indications for which it is approved, a sponsor must submit an NDA supplement. Supplements for approval of an additional use or indication are called efficacy supplements or supplemental new drug applications. After review and approval by FDA, the new indication is added to the approved labeling and can be promoted by the drug's manufacturer.

THE IMPORTANCE OF THE EFFICACY STANDARD

The fundamental precept of drug regulation in this country is that drug products must be proven safe and effective before they can be sold. The requirement that drug products be proven effective, on the basis of adequate and well-controlled clinical studies, was first adopted by

Congress in 1962. In adding the concept of effectiveness to the Federal Food, Drug, and Cosmetic Act (FDC Act), Congress specifically intended that the efficacy requirement would apply not only to the initial indication for a drug, but also to indications that come to light after the initial new drug application has been approved. 108 Cong. Rec. S22044-46 (daily ed. October 3, 1962); S. Rep. No. 1744, 87th Cong., 2d Sess. Part 2 at 267, 271 (1962).

The addition of the "efficacy standard" revolutionized drug development and approval, not only in the United States, but worldwide as well. It clearly established that data from adequate and well-controlled trials, independently evaluated by experts at FDA, were necessary to demonstrate effectiveness. When FDA worked with the National Academy of Science's National Research Council to review the effectiveness of drugs marketed in the United States before the effectiveness standard was established by Congress in 1962, 1,124 of the 3,443 drugs on the market, being marketed for various claims, were pulled from the market because they were not effective. Data of lesser quality, anecdotal reports, and poorly controlled observations do not suffice because these data or reports may be wrong or may not be an adequate basis to reach a sound conclusion. Even when such data or reports suggest efficacy, they fail to provide important guidance in areas critical to the effective use of a therapy such as dosage and patient selection and management. This in no way suggests that clinical observations are always wrong or are not of value. Alert clinicians have been the source of hundreds, probably thousands, of insights about the indications for which drugs may be useful and how best to use these drugs. But these observations need evaluation in controlled trials.

The wisdom of the efficacy requirement has been borne out repeatedly. For example, many drugs approved before 1962 turned out to be ineffective when, after 1962, they were studied for effectiveness. The solid foundation that is laid down by the efficacy standard is one of the main reasons that there is such a strong sense of confidence in the drug products that are on the United States market today. Recognition of the critical value of controlled trials is not confined to those in the United States. It is a world-wide regulatory standard and is the standard expressed repeatedly in scientific assessments and reports of all kinds -- clinical reports, editorials, and in academic and government evaluations.

OFF LABEL USES

The history of the FDC Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Thus, once a product is approved for marketing for a specific use, FDA generally does not regulate how, and for what uses, physicians prescribe that drug. A licensed physician may prescribe a drug for other uses, or in treatments, regimens, or patient populations, that are not listed in the FDA-approved labeling. Uses that are not approved by FDA are referred to as "off label", "unapproved", "unlabeled," or "extra-labeled" uses.

The extent of off label use varies from one drug class to another. For example, off label use is very high for oncology drugs, yet much lower for many other drugs. FDA recognizes that, in certain circumstances, off label uses of approved products are appropriate, rational, and accepted medical practice. Off label uses, particularly for oncology, rare diseases, and pediatrics, can be of

great value. Some off label uses have been of great historical importance. Use of beta blockers in hypertension and angina preceded labeling for these uses by many years. It is inevitable that there will be preliminary support for off label uses before definitive information becomes available. Physicians confronted with patient needs, may choose to act on such data, especially where there are no good alternatives.

Physicians have extensive access to information about off label uses through compendia, textbooks, journal articles, continuing medical education program symposia, and professional meetings. Physicians also have access to a number of data bases that provide information about off label uses. For example, the National Cancer Institute's Physician Data Query (PDQ) system is an excellent source for oncologists to obtain information about current oncologic therapies. The National Library of Medicine (NLM) offers a Medical Literature Analysis and Retrieval System (MEDLARS), which is a computerized system of databases and databanks pertinent to biomedical research and patients. Also, NLM currently offers free access to three databases related to AIDS. FDA does not regulate a physician's access to any of these sources of independent off label use information -- no matter how preliminary the data may be. Also, FDA does not prohibit a manufacturer from providing a physician with information about off label uses if the physician makes a specific unsolicited request for the information. It is important to good medical practice, however, that physicians have access to accurate information about drugs and how to use them. Without accurate information, physicians cannot help ensure their patients obtain the correct therapy in the correct dose. By seeing to it that such information gets on the

label, we can be better assured that wide dissemination of that information is made to everyone who could benefit from such information.

Unlike with the practice of medicine, the FDC Act specifically directs FDA to regulate the promotion of drugs. Promotional materials are considered unlawful if they promote an unapproved use for the product; contain claims relating to the dosing, safety or effectiveness of the product that are inconsistent with the approved labeling; or if they lack a fair and balanced presentation of information, i.e., of benefits and risks. Were companies allowed to promote uses of drugs that have not been proven effective, they might promote uses that do not work or are dangerous. In addition, they would have no incentive to conduct or fund the necessary scientific research and to present data to FDA to verify the safety and effectiveness of those off label uses. In fact, because the Agency might determine that the new use is not supported by the evidence, there would be an incentive to avoid FDA review. A question could be asked as to why a drug company would undergo the expense of actually studying whether a cancer drug works for crippling arthritis if it could promote the drug for arthritis based on preliminary evidence, particularly since a thorough study might fail to establish efficacy for arthritis?

In a world where off label uses can be promoted legally, manufacturers would have an incentive to do the minimal amount of studies necessary to obtain approval for the first, narrowest/easiest indication and then heavily promote the product for other broader (and possibly more speculative) uses. This is precisely the scenario that Congress sought to prevent when it added the effectiveness requirement to the FDC Act.

WHAT WE ARE DOING TO ENCOURAGE EFFICACY SUPPLEMENTS

As previously mentioned, a subsequent indication is added to the labeling through the submission, review and approval of an efficacy supplement. Once an efficacy supplement is approved, that indication can be promoted by the drug's manufacturer.

There already are several good reasons for drug companies to submit efficacy supplements. These include the following:

- The manufacturer can promote the use, whether through the use of journal articles or other means.

- Approval usually ensures that third-party payers will reimburse for the use, as insurance companies virtually always pay for approved uses of drugs and devices.

- As health maintenance organizations (HMOs) continue to grow in size and number, a sponsor's ability to get its drug included in the HMO's drug formulary will be significantly enhanced.

- The physician, via the approved labeling, is given more complete information about the drug's uses and proper dosing as well as its contraindications, adverse effects, and other important information about the manufacturer's product.

- And, drug companies can present the FDA findings to drug approval bodies in other countries, thus enhancing their ability to gain approval (and reimbursement) for uses in other markets.

Despite such incentives, however, many indications remain unlabeled, presumably because the incentives are not perceived to offset the resources that would be required to obtain approval for a new indication. There appear to be two primary reasons for the failure of the sponsors to pursue approval of new indications . First is the concern that millions of additional dollars will be required to conduct new clinical studies to establish the safety and effectiveness of a use. Second is the concern that efficacy supplements are a lesser priority for FDA than applications for new products, and, as a result, the review process is very lengthy and is likely to erode much of a sponsor's market exclusivity. These concerns may exist in part because FDA has not been as clear as it could be about its data requirements for efficacy supplements. FDA is now engaged actively in efforts to address these concerns to encourage and expedite efficacy supplements for unapproved uses. We are doing a number of things and have several ideas for additional progress in this area. I will outline them for you:

New Initiatives at FDA

Earlier this year FDA assembled a task force to examine, in depth, the broad range of issues that influence whether a supplemental indication makes it into a product's labeling. The Supplemental Indications Working Group ("the Group") has focused on identifying barriers to sponsors'

submission of supplemental indications, and means to lower or eliminate identified barriers. The Centers for Drugs, Biologics, Devices, and Veterinary Medicine are each represented on this task force.

The Group is studying a variety of strategies to encourage the submission of supplemental applications, and developing a clearer articulation of the scientific standards used by the Agency in assessing the safety and effectiveness of new indications.

Certain general themes have emerged from the Group's deliberations. Traditionally, FDA has perceived its role to be a somewhat passive one, reacting to data only when a sponsor submits it. There is a growing recognition, however, that to address the problem of unlabeled uses effectively, FDA should adopt a much more active role in identifying important supplemental indications, facilitating their study and evaluation, and, if effective, incorporating those uses in the labeling. There also is awareness that the best solutions to the problem will be achieved by getting as many of the affected constituents as possible involved in creating strategies to get new uses into labeling. It is apparent; however, that for products that lack marketing exclusivity and for supplemental indications that benefit only small populations, no combination of strategies reliably will induce commercial sponsors to pursue supplemental applications. To get these uses into labeling likely will require allocation of public funds, particularly where additional data would have to be developed to demonstrate that a use is safe and effective.

Current proposals under discussion envision that we become: (1) more active in identifying unlabeled uses, preliminarily assessing the data that support a use, and actively encouraging commercial sponsors and other interested parties to participate in pursuing approval of identified uses; (2) more accessible and responsive to the broad array of constituents that have an interest in whether uses are in labeling; and (3) more transparent in the standards we apply in making decisions concerning safety and effectiveness. Proposals under consideration include the following:

Identifying Unlabeled Uses:

- That the Agency take a leading role in coordinating with patient groups, commercial sponsors, health care professional organizations, and health care purchasers to identify the most important unlabeled uses and develop strategies as to how to get supplemental applications submitted for those uses that seem to be supported by existing data, and to develop needed data for uses that need to be more fully evaluated. Although off label use is seen in all medical specialties, it is most widespread in certain areas, such as oncology and pediatrics. Beginning with those specialties, we will work with practitioners and their specialty associations to identify the off label uses that are most appropriate. We then will present those findings to the sponsors of those drugs and urge them to work with us to get the indications in the labeling.

- For products that are off-patent and for which there are likely adequate data to support an unlabeled use, that the Agency explore ways independently to assemble and evaluate data

on unlabeled uses and, where the data are sufficient to support a use, make the data publicly available and invite potential sponsors, commercial or otherwise, to submit applications based on that data.

- For products that are off-patent and require additional data to support an unlabeled use, that the Agency explore ways to engender cooperative research efforts among interested constituents to develop needed data.

Agency Accessibility and Guidance:

- To address uncertainty about the type and quantity of information that is needed to establish safety and effectiveness for an efficacy supplement and the impression that data requirements are very high, that the Agency publish guidance that makes clear the scientific standards that are used in determining safety and effectiveness for efficacy supplements.

- That the Agency take steps to assure that the case-specific guidance and support it provides to sponsors and potential sponsors of supplemental indication applications is comparable to the guidance that is afforded sponsors of new drug applications (first approvals). This proposal would provide sponsors a ready means to clarify Agency data expectations for unlabeled uses and thus help sponsors make better informed decisions as to how to allocate their resources. Also, in conjunction with our commitment to adhere to the Prescription Drug User Fee Act of 1992 (PDUFA) time frames, it will reinforce the

Agency's commitment to not treat supplemental indication applications as lesser priority applications.

The goal is to describe in a guidance document situations where different data submissions than the standard data (i.e., two adequate and well controlled studies of the same use with full data available) are sufficient to establish safety and effectiveness for a new indication. This in no way reflects a retreat from existing safety and effectiveness standards, but, rather, describes a sound scientific basis for when data, other than data that exactly replicates a finding, are nonetheless adequate to establish the validity of a finding. Examples of situations where different data submissions than the standard data may support a safety and efficacy determination include the following:

- When the drug has been studied in other disease phases:

For example, some oncology products are first studied and approved for use in late stage, refractory cancers, i.e., those that have not responded to other available therapies. A single well-controlled study of a drug in an earlier stage of the same tumor, together with the studies of the later stage of the disease, might support a new indication.

- When the drug has been studied in a closely related disease:

For example, for an oncology drug that has shown anti-tumor activity against one type of tumor, there is a strong presumption that it could be active against other types of tumors. Thus, a single well-controlled trial might support its use for another type of tumor. Similarly, for an antibiotic that has demonstrated activity against one type of infection caused by a particular organism, a single well-controlled trial of the drug in another infection caused by the same organism, in conjunction with evidence showing that the antibiotic achieves adequate blood levels at the site of the other infection, might support its use for the other infection.

- When the Agency does not have access to full reports of data, but there are multiple published reports in the literature of studies of adequate design and consistent results:

It is the Agency's belief, based on substantial experience, that full access to study data is very important, and journal peer reviewers rarely have full access to the raw data that are the bases for the manuscripts they review. Nonetheless, when there are multiple published trials of good design and consistent results, the consistency of results may overcome FDA concerns about not having access to underlying data to verify results or analyses. However, it is probably more common that easily available selected critical data (e.g., the protocol, data tapes, etc.) might be sufficient to allow review.

There are many more examples that illustrate when existing data may obviate the need to exactly replicate a study finding and there is an effort underway to compile these examples in a useful guidance document. It is hoped that, by explaining the relevance of data that may already exist,

this document will clarify that the Agency's data expectations for new indications of already approved products are perhaps not nearly as great as some sponsors perceive them to be.

FDA also is examining mechanisms and resource requirements for implementing the strategies which ultimately are decided upon.

Expediting Review of Efficacy Supplements

As you know, PDUFA is helping resolve the problem of timely reviews for drugs and biologics. Under PDUFA, for the applications submitted in FY 1997, the Agency will perform a complete review and take an action on all drug and biologic applications (NDAs and PLAs) within 12 months of submission for standard applications and within 6 months for priority applications. These review performance goals apply to efficacy supplements as well. In fact, under PDUFA, for NDAs, PLAs, and efficacy supplements, the Agency has exceeded the interim goals established by Congress. For applications submitted in FY 1994, the Agency reviewed and acted upon 96% of the NDAs and 77% of the efficacy supplements on time. The interim "on time" performance goal, agreed by Congress and industry, for this group of applications was 55%.

For those applications submitted in FY 1995, FDA continues to far exceed the goals established under the user fee program. The established performance goal for the group of applications submitted in FY 1995 was to be "on-time" at least 70% of the time. In fact, already we have reviewed and acted upon 89% of the NDAs in this group and if we act within the PDUFA

timeframe on those remaining in this group that are not yet overdue, the final performance for NDAs in this group will be 99% on time. In addition, the Agency has reviewed and acted upon 90% of the efficacy supplements for NDAs within the determined time frame. The agreed performance goal was only 70%. If we continue this trend in reviewing efficacy supplements that are not yet overdue, we will be 95% on time.

We should continue our efforts to reduce review times for all applications and to improve upon them. We are working on mechanisms and policies that should decrease the number of months for review.

RECENT ONCOLOGY INITIATIVES HAVE IMPLICATIONS FOR ONCOLOGY DRUG SUPPLEMENTAL INDICATIONS

In March of this year, as part of its Reinventing the Regulation of Cancer Drugs initiative, the Agency indicated that it intended to make greater use of the accelerated approval mechanism for cancer drugs. This mechanism facilitates earlier approval of drugs for serious or life threatening conditions by allowing the Agency to base approval on well established surrogate endpoints that reasonably predict clinical benefit, such as evidence of tumor shrinkage in solid tumor disease and meaningful remission in hematologic disease, rather than requiring demonstration of actual clinical benefit, such as improved survival or quality of life. Companies more quickly can demonstrate tumor regression than increased survival time. Clinical benefit is established in post-approval studies. This accelerated approval mechanism is available for new product applications

and applications for new uses of already approved products for cancer therapies to treat incurable, advanced, or metastatic disease in patients without satisfactory alternative treatments.

This accelerated approval mechanism already has been used effectively. In June of this year, FDA approved a supplemental new drug application, and the first therapy shown to improve neurological recovery and decrease disability in adults following acute ischemic stroke, the most common type of stroke, caused by blood clots that block blood flow. FDA approved this supplemental application for the stroke indication in less than three months. The drug, Activase (altephase), a genetically engineered version of tissue plasminogen activator (t-PA), already was approved as a blood clot dissolver to treat heart attacks and to dissolve clots in the artery going to the lungs. The data supporting the approval of altephase as the first therapy for stroke came primarily from a five-year clinical trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS).

Pediatric Labeling

We already are demonstrating how relatively limited data can be an adequate basis for pediatric labeling. In December 1994, we promulgated new regulations that provide, in certain cases, for pediatric uses to be included in the approved labeling without new clinical studies. Pursuant to these regulations, when there is sufficient basis to conclude that the course of the disease and the effects of the drug are sufficiently similar in children and adults, sponsors can rely on existing studies in adults for evidence of effectiveness yet carry out studies of the drug's course through the body (e.g., blood and tissue levels) so that the proper dosage for the use of that drug in

children can be established. This regulation also explains about the need to submit additional information supporting the pediatric use (e.g., postmarketing data, safety data, pharmacodynamic data) in order to show that the drug can be used safely and effectively in children. A guidance document has been published to assist sponsors in submitting these pediatric labeling supplements.

Also, CDER has begun focusing on the pediatric population throughout the clinical drug development process, and we are integrating discussions of pediatric uses with sponsors throughout the IND and NDA process. We also are working on more detailed guidances to sponsors regarding early drug development, clinical trials and data review that may have pediatric indications.

CDER also has been working with Pediatric Pharmacology Research Units (PPRU) in industry regarding the development and conduct of clinical and pharmacokinetic studies of drugs in the pediatric population. CDER has proposed clinical trials on specific drugs or pediatric formulations without commercial sponsorship.

Office of Orphan Drug Development

As you can see, the Agency is committed to improving the way efficacy supplements are reviewed; however, nothing points out the difficulties associated with efficacy supplements better than drugs for rare diseases. While the Orphan Drug Act (ODA) has been called one of the most successful pieces of legislation ever written, its effect on the number of supplements submitted has

been minimal. The ODA's most powerful incentive is it's marketing exclusivity clause. Once an orphan drug is approved, exclusivity gives sponsors legal protection against introduction of an identical competing product for seven years. In addition, FDA's Office of Orphan Drug Development (OPD) assists in protocol design, and the ODA allows a sponsor of an orphan drug to claim 50 percent of clinical trial costs as a credit against taxes owed.

But, of the 131 drugs approved since the passage of the ODA in 1982, only two have been supplements. Most of the approvals have been for new chemical entities which have taken advantage of the exclusivity provided by the ODA. The tax provisions which allow a 50% tax credit for clinical trials are used infrequently according to the Internal Revenue Service.

Grants for research on orphan drugs are available under the ODA. The grants provision is aimed at academic researchers and at smaller companies. Approximately 25% (64/267) of OPD grants have been for investigations on new indications for approved drugs. The grant program is used almost exclusively by the academic community, and few pharmaceutical companies have been willing to submit the results of these studies to change labeling. Therefore, for small populations, neither tax credits nor completed studies seem to provide enough incentive for submission of supplemental indications. The one situation in which there is some activity by larger companies is when a patent is about to expire. A manufacturer will occasionally attempt to preserve a portion of the drug's market by obtaining the seven years of exclusivity provided by the ODA.

PROBLEMS WITH OFF LABEL USES

With these initiatives we hope to get more off label uses that are well substantiated on the label. FDA has found that the widespread use of unapproved indications of drugs raises significant safety concerns. Even under current law, which prohibits the promotion of off label uses, we know of a number of instances where physicians used drugs for off label uses that resulted in disastrous consequences.

For example, the drugs encainide and flecainide were approved in 1985 and 1986 for life-threatening and symptomatic arrhythmias, which are abnormal rhythms of the heart. In the 1980's, physicians prescribed these two drugs and other antiarrhythmic drugs for heart attack victims who were experiencing ventricular premature complexes (VPCs), a type of asymptomatic or minimally symptomatic arrhythmia. (Asymptomatic arrhythmias are arrhythmias that can be detected by tests, but which the patients do not feel.) These two drugs were especially popular because they were effective at suppressing VPCs and appeared to be well tolerated. These patients were treated because it was known that patients with VPCs after a heart attack were more likely to die suddenly. By suppressing the VPCs, physicians hoped to reduce the risk of death. This off label use, which was supported by published peer-reviewed journal articles linking high VPC rates to mortality, appeared "logical." After becoming aware of this widespread use, the National Institutes of Health decided to study the effectiveness of encainide and flecainide in these patients. Previously it had never been shown that treatment of VPCs was beneficial to these patients. To the surprise of almost everybody, that study demonstrated not only that the drugs

were ineffective in reducing the risk of death but that the drugs were actually harmful in patients for whom it was being prescribed off label -- increasing the risk of death by two and one half times compared to patients receiving the placebo. If these unapproved uses had been heavily promoted by drug companies, it is estimated that thousands more unnecessary deaths would have occurred each year. To compound this problem, there are other therapies that are known to be effective for this condition.

Another example relates to the widespread off label use of a class of drugs called calcium channel blockers (CCBs). These drugs are effective for patients suffering from high blood pressure or angina, which is chest pain caused by insufficient oxygen to the heart muscle. In addition to this approved indication, CCBs have been widely prescribed for use in patients who have had a heart attack, but have no symptoms. CCBs have no established role, however, in this patient population despite publications that could be interpreted as supporting this use. These patients do, however, benefit from another class of drugs, beta-blockers, which are known to reduce mortality by 25-30% after heart attacks. Because CCBs and beta-blockers generally should not be used simultaneously, patients are receiving CCBs in lieu of clearly life-saving beta blockers. Many, probably thousands, of lives are lost each year because a drug with no known survival benefit is being used for an unapproved use in place of a drug with known value. Widespread promotion of this use would make the problem even worse.

It is important that solutions to the problem of unlabeled uses not compromise either the efficacy or safety standard, for such solutions would be tragically nearsighted. So, while we support

efforts to facilitate getting more indications into product labeling when the indications are supported by adequate data, we strongly oppose proposals that, in seeking to address the unlabeled use problem, either directly or indirectly compromise the efficacy standard. We would oppose any initiative to lessen the efficacy standard for supplemental indications. We also would oppose any initiative that seeks to address this problem by allowing sponsors to promote unlabeled uses. Such promotion diminishes the efficacy standard by reducing the incentive to adequately study new product uses.

Adequate and well-controlled studies, as currently required, are a major part of ensuring the first-rate medical care that the health care system in this country provides. Consider some of the additional uses that FDA has approved on the basis of such studies -- for example, timolol, propranolol, metoprolol, and atenolol to improve the survival of heart attack patients, taxol for breast cancer, and interferon-alpha 2b for chronic hepatitis B and C. Without the requirement to submit clinical studies to prove that drugs are safe and effective for their intended uses, it is far less likely that we would know the true value of these drugs in decreasing mortality in heart attack patients, in delaying or preventing breast cancer recurrence, and in treating chronic hepatitis B and C.

CONCLUSION

Public confidence in drug therapy has been built on the recognized rigor of FDA's approval process. FDA recognizes that there are important uses of drugs that are not on the label. Having

information on the label about all conditions for which the drug is effective and how to use the drug for that indication is important to public health. It is equally important to public health to not have drugs being used for indications for which we have no assurance of safety and effectiveness. We know there have been some problems and we are working on improved means for getting well documented indications on the label. We are facilitating this by a number of initiatives for all supplemental indications, including initiatives particularly geared to getting oncology and pediatric indications on the label.

Our obligation to the public is to give physicians and other health care practitioners accurate information in order for them to give patients the best care. An active medical and research community means that uses of previously approved therapies will continue to be recognized. While FDA generally does not sponsor these activities, we do want to ensure that their value is fully applied for the public's benefit. The supplemental application and review process can help ensure that the information generated by medical research is accurate, and in fact, does represent a safe and effective new use for the public. The labeling of the drug for that new use, in turn, assures that there is consistent and wide dissemination to practitioners about that new use and proper dosing. With such information on the label, we can give practitioners the information they need to get the correct therapy to their patients.

There are many constituencies interested in this issue, some of whom you heard from today. We appreciate the Subcommittee's interest in this important issue, and welcome the opportunity to work with the Subcommittee and affected constituencies in developing ways to have drug

products' labels more completely and accurately reflect clinical usage that is safe and effective. All of us will benefit from such an effort.

I would be happy to answer any questions.

Mr. SHAYS. Thank you, Dr. Friedman. Before I ask a specific one, is there any comment you want to make? You were here for the first panel, correct?

Dr. FRIEDMAN. Yes.

Mr. SHAYS. And I would also invite either Dr. Woodcock or Mr. Schultz to respond as well. So any observations to start, because it might save me asking the questions.

Dr. FRIEDMAN. If I might make just some general comments and then—but I don't want to waste your time either and want to make sure that we get to your questions.

Mr. SHAYS. No; but we wouldn't have asked the questions—the questions we asked of the first panel are still on the table, and I need observations.

Dr. FRIEDMAN. Good.

Mr. SHAYS. So I am relating it to the first panel and the questions we asked, whether it was Mrs. Morella or Mr. Towns or Mr. Souder or myself. Any responses that you would have made that you wanted to make when we were asking those questions?

Dr. FRIEDMAN. Thank you, sir. I see this problem of how to get more information onto the label as much as anything an epistemologic question of what is good data and how does one deal with those data.

The fact is that for some supplemental applications the agency can have a much simpler, a much more rapid, much less expensive means of asking for the proper data and making good decisions. There will, however, be some supplemental indications that are so complicated or where the use entails such danger that they will, in fact, be as large or even larger perhaps than the primary indication.

The agency is very committed to improving this system. We, as you know, last spring announced in our oncology initiatives that we were accelerating approvals not just for primary indications, but we identified ways in which for cancer products supplemental indications could be approved through an accelerated mechanism. And we have made some progress in that regard.

I think that in addition to the incentives and disincentives that you noted, a very important one that was mentioned but perhaps didn't get enough attention was the increasing importance of pharmacoeconomic considerations.

When a pharmaceutical industry makes certain presentations to the pharmaceutical boards of HMO's or managed care organizations, and we see a very powerful incentive that if the FDA has reviewed these supplemental indications for that product and has approved it, it makes that presentation to that pharmacy board or formulary board that much stronger. And we see that as an important new incentive as well.

I would be happy for Mr. Schultz or Dr. Woodcock to elaborate.

Mr. SHAYS. Sure. Any comments either of you would like to make?

Mr. SCHULTZ. I will make a comment. I think my general reaction to the panel discussion was that it accurately and very capably reflected a lot of the difficult issues that you are grappling with, and, I think the questions did as well.

I think that behind all this is the 1962 efficacy standard where Congress made a decision that when a drug goes on the market and when a company promotes a drug, it must first prove that it is effective. But at that time, Congress also had to grapple with the question of how involved the Federal Government is going to get in a doctor's decision about prescribing a drug.

I think initially when one doesn't think about it, it probably seems like the doctor shouldn't prescribe the drug unless the drug is proven to be effective. But, I think, as some of the panel discussion reflected, that is just not realistic and it really does not advance the best practice of medicine.

A compromise was reached that we would be very rigorous in terms of the label, but once the drug was on the market, we would leave a lot of discretion to the doctor. That is not to say that we are saying that the doctor should do anything he or she wants, but the discretion is there.

And as we have gone around and around it, that may be a pretty good place to be, even though it is not intellectually totally consistent.

Mr. SHAYS. Mr. Schultz, I really appreciate that response because I think that is a very logical and clear explanation of why we are here where we are today, and it may be a justification to continue, given the alternatives may be not as good. And so I appreciate you articulating it in that way.

I am struck by the fact that, in a sense, we do, obviously, have two standards. It weights primarily more toward efficacy, I make an assumption, than it does to safety because I make an assumption that—and correct me if I am wrong—that for a drug to get on the marketplace, for the most part, we really are pretty convinced it is safe on the marketplace. But, obviously, you can misuse a drug so I am now going to contradict myself. You could use it in a way that could be totally destructive. But we make an assumption then that it is unlikely we would use the drug that way.

The bigger question, and I am now making another assumption, is it is really more an efficacy issue than a safety.

May I first just ask this question for the record? It is my understanding your primary statutory responsibility is to prove that a drug is safe and to prove that it is effective for the purposes for which it would be prescribed. Is that your primary statutory responsibility?

Mr. SCHULTZ. Or promoted.

Dr. FRIEDMAN. Labeled; yes.

Mr. SHAYS. Would you agree that the secondary use of drugs tends to be more an efficacy issue than a safety issue?

Dr. FRIEDMAN. No, sir.

Mr. SHAYS. I saw, Dr. Woodcock, you shook your head the most, so I am going to choose you first.

Dr. WOODCOCK. When FDA approves a drug, we approve it as safe for its intended use. And that is a very different statement than saying the drug is safe overall. Actually, no pharmacologically active agent is totally safe.

And what we really do when we are approving a drug for an indication and a group of patients, is saying that the benefits, the demonstrated benefits, outweigh the demonstrated risks. As you go fur-

ther away from the target population and the indication, you have less and less knowledge that the actual benefits are going to outweigh the risks because you haven't quantitated them as well.

We have instances of off-label uses that have occurred in the recent past that actually caused mortality in the people they were used in although, intuitively, those uses seemed very close to the labeled use.

Dr. FRIEDMAN. May I?

Mr. SHAYS. Yes; thank you.

Dr. FRIEDMAN. Another example of that, to help put this in perspective, and it is a recent example. There is a drug which is currently marketed, tissue plasminogen activator, which is a very powerful biologic therapy for use in patients who have coronary artery occlusions. So for patients who have a heart attack, there are some of those patients who benefit very, very substantially from this product.

But it was also noted that there are some patients who have strokes, vascular accidents in the brain, where this treatment might be useful. There are not good treatments for patients who have strokes and, therefore, this was a very high priority for the agency to look at it, even though the drug was on the market. We received an efficacy supplement for this, reviewed it in record time, 89 days even though it was a very large clinical trial, because we were concerned to get it on the market.

The reason I point this out is if this drug is used in a certain kind of stroke patient, the bleeding is much worse, the patients have a devastating neurological consequence, and many of them die. If it is used in the right kind of stroke patient who have certain characteristics, then the improvement in those patients is statistically significant and those patients benefit.

So that here is a drug that was on the market. It was clear what the benefits and risks were for heart attack patients. It turned out to be entirely different for another group of patients. And that is why having that labeled information allowed the company to educate physicians how to use it meant that physicians would be using it in a much more appropriate way.

So there are a lot of instances where there is real risk as well as real benefit in a supplemental indication.

Mr. SHAYS. I make an assumption that—I usually expose my ignorance but I do learn from it and, hopefully, it has some value when we write our report. I make an assumption that we are first likely to test something on an animal before we test it on a human being. And then, we are going to test it on human beings under a protocol that is fairly restrictive for those whom the drug is administered to. They know the risks and they accept the risks.

And I make the assumption again that this is a process that has to go through the FDA, this whole protocol process. Is that correct?

Dr. FRIEDMAN. In terms of preclinical?

Mr. SHAYS. Yes; preclinical, before you bring it on the marketplace.

Dr. FRIEDMAN. There is a body of preclinical data that is presented at the time the new product is filed.

Mr. SHAYS. And does it usually begin with animals before people?

Dr. FRIEDMAN. Almost always. Yes, sir.

Mr. SHAYS. Now, I then make an assumption that we would more likely test something, if a human being is involved, that it is going to be an adult before it is a child.

Dr. FRIEDMAN. In general, that is absolutely correct.

Mr. SHAYS. So, but for drug companies to bring a particular product to the market that is supposedly directed at children, then eventually it would be tested on children before it came to the marketplace, adults to children?

Dr. WOODCOCK. Do you want me to answer that?

Dr. FRIEDMAN. Please, go ahead.

Mr. SHAYS. What I am trying to understand is why we see a lot of off-label use for children. And I am making an assumption that I want to clarify that we are not as likely to utilize a drug on a child in the protocol process.

Dr. WOODCOCK. Early in drug development, ordinarily, testing is initiated in adults. And what you said is true for non-life-threatening diseases of children; that adults are tested and we have some basic safety information or maybe quite a lot, or even the drug might be approved and some efficacy information before testing it in children.

But for diseases where children are targeted and for diseases where children have life-threatening consequences, the pediatrician community has really stood up and said these drugs for life-threatening diseases in children should be tested early in children; children have the same need for these kind of drugs. And so, ordinarily, they will be tested first with a very early safety testing in adults and then childhood testing may start.

Mr. SHAYS. Now, this goes back to Mr. Schultz's statement that considering the extraordinary cost and time process of bringing a drug into the marketplace, a rare disease is just not going to get attention, so it is logical to me that you would see off-label drugs be more involved. I am not surprised by the statistic that it is close to potentially 80 percent for rare diseases.

But, what I would like to know is what is the protocol for a doctor who has this interest in a rare disease looking at a drug and then using it as off-label? What is the protocol and what is the potential liability to that doctor?

Dr. FRIEDMAN. Perhaps I should have Dr. Haffner, who is in charge of our orphan products, answer that.

Mr. SHAYS. Sure. We welcome you to come up. You can just pick up the mike if you like or you can just sit down a second. Why don't we bring an extra chair, Tom, and then we can do a musical chair if someone else comes up.

Thank you, Doctor. Identify yourself again when you are sitting down just so we know.

Dr. HAFFNER. Thank you. I am Marlene Haffner. I am director of the Office of Orphan Products Development.

Mr. SHAYS. Did you hear what the question was?

Dr. HAFFNER. Would you restate it again, please?

Mr. SHAYS. I was hoping you would say yes, you heard what the question was. I think the question involved the issue of rare diseases, the issue of a doctor looking for a secondary use for this drug, taking a drug on the marketplace and now having a secondary off-label use for it, and the question of protocol and also the

question of potential liability to that doctor if he or she misused that drug.

Dr. HAFFNER. As has been stated many times already today, certainly a physician that thinks for good reason that a product that is available to him or her may work in a particular disease may use it in that disease. And they will think that from literature reports, from reading the journals, from courses, et cetera, and may well try it in that situation.

Mr. SHAYS. As to the protocol, do they have to tell the patient that this is an off-label drug and so on? Do they have that kind of requirement?

Dr. HAFFNER. They don't have that requirement. They may well do that.

Dr. WOODCOCK. It depends on the institution. Some academic institutions may have those requirements but, generally, in the practice of medicine informed consent for an off-label use isn't necessary.

Mr. SHAYS. I'm not looking for more regulations and so on. I mean, but it would seem to me that this is one area that there could be some common ground because, obviously, if we are using something in an area where, Dr. Woodcock, you pointed out a drug is safe for the use it is intended, it would seem to me that, at least, for the safety issue if not for the efficacy issue, there would be some protocol that said this is a drug that is not labeled for this use, but based on my belief, I think it may be effective in your case.

Dr. FRIEDMAN. Maybe I should just add one other thing. And I don't mean to overstate this, but there is real concentration of research at certain institutions for certain kinds of diseases, as you well recognize.

And because academic centers may be devoted to the study of unusual metabolic diseases, unusual neurologic diseases and so forth, rare diseases often are studied at institutions that have very formal research structures in place and may be supported by grants, sometimes given by us and sometimes given by NIH. Under those circumstances, there is a protocol. There is informed consent and so forth.

Mr. SHAYS. I hear you. I hear you. That would seem logical, I mean, for a variety of reasons.

Dr. FRIEDMAN. Sure.

Mr. SHAYS. But I'm just saying, you know, our weighing in on this, and we may decide to say in our report, and it wouldn't be based on one hearing, let me assure everyone here, that we should just not deal with this issue; that, you know, the recommended solution may be worse than the present circumstances. But it would strike me that if we got into any area, this might be one that we would.

Dr. HAFFNER. The treatment of one patient by a physician seldom is reflected in a protocol; on the other hand, our office has a grants program wherein we publish in the Federal Register annually requesting clinical trials for certain rare diseases. And under certain circumstances, we have even said we would like clinical trials for certain drugs for certain diseases if we know that a drug is being used, if we know that there is a particular need for a dos-

age form of a particular drug. That is not the usual, but it has been done.

Mr. SHAYS. Thank you. Yes.

Dr. WOODCOCK. I would like to make a clarifying comment about off-label use. Off-label use is certainly very prevalent in orphan drugs and cancer and so on, but I don't think you can estimate the use across general medical practice.

As Dr. Haffner said, for the single patient, if someone has a migraine and they have exhausted the conventional therapies that are approved for the prevention of migraine attacks, a doctor may well go onto other kinds of blood pressure medicines or other medicines that are approved for something else to try in that patient. We don't know the extent of this. There are no good studies. But we believe it is fairly widespread.

Mr. SHAYS. Thank you, Doctor. I am beginning to realize that maybe when I use protocol I should have used the word "ethics".

Dr. WOODCOCK. Informed consent, I believe is what you meant.

Mr. SHAYS. Yes; OK. And just make a reference again to what your view is on informed consent. I'm sorry. You triggered something and then I began to get off your message.

Dr. WOODCOCK. You asked, I believe, that if in rare diseases patients had informed consent.

Mr. SHAYS. In any disease where the drug is used for an off-label use that hasn't even been established—I mean, they are going into new territory—is there any requirement that a patient be told that this is a recommendation, and should there be, is my question. And I would welcome any of the three of you responding.

Dr. WOODCOCK. There is no recommendation but, as I said earlier, certain institutions may.

Mr. SHAYS. I understand that.

Dr. WOODCOCK. There is no Federal regulatory requirement.

Mr. SHAYS. I understand that. If I was a large institution, I would have more protocols and more ethical standards to make sure I covered every base. That's not what I'm asking.

Doctor.

Dr. FRIEDMAN. Excluding formal studies, it is considered to be medical practice and physicians inform patients about side effects of treatment as they usually do. But in terms of formally signing an informed consent document, I think that's a rarity. I think it is very uncommon.

Mr. SHAYS. OK. And the question is: Should there be? You know, I realize that if you don't know the answer, I am not going to—I wouldn't want you to respond to a question like that unless you have given it a lot of thought, but I would think that you have given it some thought.

Dr. FRIEDMAN. I don't think we've given it sufficient thought. It is a very good question and a very complex question. I don't feel that I have given it enough thought.

Mr. SHAYS. OK. I've been having a little debate with my colleague here on five questions that she wants me to ask for the record. And I have never asked five questions written, but I am going to do it. You better be right.

Dr. FRIEDMAN. We'll do our best to answer them, sir.

Mr. SHAYS. But I'm afraid we may be here all day. How does the lack of efficacy and dosage information on products for which there is extensive off-label use affect the quality of care for pediatric, cancer, and rare disease patients? That's what I asked the first time around.

Dr. FRIEDMAN. Well, I think each of those are different in complex populations. If you take certain subgroups of patients, for example, pediatric oncology patients, the amount of care that is given to those patients is extraordinarily centralized into a relatively small number of physicians and a relatively small number of institutions. The kind of information that they share with one another with electronic data bases and others is really exceptional.

And, so, I think that for a group such as pediatric oncology patients, the majority of whom are treated in formal protocols and in academic institutions or other tertiary care institutions, that there is relatively little difference in the care of those patients.

I believe that for other of the populations that you have mentioned, it really becomes the quality of care that those individuals are receiving, and I don't think we have good data to say whether or not those patients would benefit more or whether or not they suffer.

Let me make a general statement, which is, leaving aside the incidence of this and leaving aside what the theoretical concerns might be, we think that there are powerful reasons to have the label reflect as accurately as possible current care and, therefore, we are moving to that. If this is a small problem, if it is a large problem, we still think it is a problem which we can deal with not 100 percent, but that we can help in a very meaningful way. And we are committed to that.

Mr. SHAYS. OK, question two: Why did the FDA take from April 27, 1993 to February 7, 1996, to compile a list of the most prevalent off-label uses of drugs after requesting this information for 10 academic medical societies, and is this delay a reflection of the low priority the agency assigns to supplemental new drug applications and the extent of off-label use?

Dr. FRIEDMAN. I will be happy to deal with the second half of that question.

Mr. SHAYS. Sure.

Dr. FRIEDMAN. I would ask Dr. Woodcock, please.

Dr. WOODCOCK. In 1993, the agency had a task force trying to grapple with the prevalence of off-label use and requested information from medical societies and other authoritative bodies on where they thought the problems were in off-label use. That information was sent to us and we did compile it.

However, I think the question relates to the fact that our application of that to each specific disease area and so it is hard for me to answer the second part of the question. We did compile that information. We looked at it. We didn't find it as helpful as we had hoped at the time we received it. But now we are taking a second look at that and we are attempting to go through disease by disease area and try to see if there is something we can target to stimulate supplements in that area as part of Dr. Friedman's work.

Dr. FRIEDMAN. But, I think what was surprising to the agency was how few responses were gotten, that relatively few products

were even suggested. When the blanket invitation was issued to say what would you like us to consider, what do you think is worthwhile, very few specific answers came back.

When queried—and this is not a scientific sampling. This is just particular people being asked. When queried, some individuals said we would prefer not to have things designated as supplemental applications because that will then call into question what is and what it is not on the label and we prefer the ambiguity of the current situation. Others said there isn't a problem now and, therefore, we don't want to do this.

Another part of this issue is—and I don't mean to oversimplify this and you need to ask industry directly—but, at least, two things occur to us from an industry perspective as to why there is less enthusiasm for submitting a supplemental indication.

One is that the penetration of the market is so complete and the acceptance of the drug is so good right now that they don't need—there is no promotion. There is no other incentive that they would have by submitting an application. This is a good product. Its use is effective. People widely accept it. Therefore, why should they go to the trouble to submit that paperwork?

Mr. SHAYS. Let me just ask you, in other words, what I think I hear you saying is that the two negatives for not being on label is they can't promote, but you're saying they may not have to.

Dr. FRIEDMAN. At least one situation they may not have to because it is already widely recognized as a good treatment; everybody likes it and uses it.

Mr. SHAYS. And then the only other incentive for them to do it would be is if patients weren't being reimbursed.

Dr. FRIEDMAN. There are others as well. But the second, as I see it, major disincentive is that there is a small economic incentive. The product may be useful. They may have some of the data.

But it may be near the expiration of whatever patent protection they have or there are generic products for this very same application, and that if a company spends the resources to get that supplemental application approved, generics may benefit from that, not necessarily themselves. And so they don't see a vested interest in doing it.

Again, there are many other incentives that companies have. I am not being critical of companies. I am just saying these are two of the disincentives that we can perceive.

Mr. SHAYS. Before I call on my colleague I just want to, for the record, get these questions on. They really do deserve to be asked.

If the agency can use its discretion to evaluate applications for AIDS with less initial clinical data and greater access for patients during the review process, why can't the agency utilize its discretion to develop more expeditious review processes for oncology, pediatric, and rare disease drugs, taking into account the special challenges of clinical trial designs to demonstrate efficacy in these populations? It's a long question, but I think you get the gist of it.

Dr. FRIEDMAN. And you are absolutely right. As I pointed out in the initiatives that we announced in the springtime, we took a major step in oncology of using objective response as a surrogate endpoint to more rapidly allow—and with a smaller amount of data

and a more easy manner—allow a company to achieve a supplemental application.

Mr. SHAYS. So, the answer would be, yes; there is nothing that restrains you from doing what you did with AIDS with other drugs?

Dr. FRIEDMAN. The answer is, we are in the process. That's correct. Yes; we are in the process of doing it. I think we can do it better and we are looking at ways of even further streamlining the application process and simplifying it.

So, I don't mean to sound arrogant and say we've already done it and it's fixed, but we are already moving in that direction. And the numbers are very clear. The review times are dropping.

The problem is not so much the time it takes to review the application; the problem is not enough applications are coming in. How can we do our part to help create an environment to solicit or to make it easier for companies or other interested parties to submit? I think that is a challenge.

Mr. SHAYS. You're talking about secondary labeling?

Dr. FRIEDMAN. Yes, sir.

Mr. SHAYS. What prevents FDA from requiring pediatric studies for NDA and SNDA submissions when drug sponsors do not include pediatric indications in their application?

Dr. WOODCOCK. What prevents us? It sounds like underlying that is the suggestion that we should require for certain drugs that there be pediatric data at the time of first approval of the drug. We don't have that requirement right now. That is true. And you would have to imagine what sanctions we would impose if that weren't the case if we had that rule.

Mr. SCHULTZ. I just want to add though, this has been suggested to us that we initially require it. And as Dr. Woodcock says, there are some complexities in terms of what we would do if it weren't submitted. We have been asked to look at this, and we are doing so.

Mr. SHAYS. The issue of literature-based information?

Mr. SCHULTZ. No; as I understand it, it is the issue of saying to the companies when you submit a new drug application to us, that if it is a drug that is likely to be used in children, particularly very young children, one of the pieces that we want is a piece that would allow us to evaluate it for children.

Mr. SHAYS. I am going on the assumption that more than three-quarters of the drugs used for kids are unlabeled. I mean, maybe I am starting with a false assumption, but I make that assumption.

Mr. SCHULTZ. I think everybody agrees that it is a high percentage.

Mr. SHAYS. Close to that? I mean, am I unrealistic to say three-quarters, basically?

Mr. SCHULTZ. I don't know the number. I believe that it is substantial.

Mr. SHAYS. The 80 percent, I think, came from studies, so I was using three-quarters. I mean, isn't it approximately 80 percent? I would like to nail this one down. I mean, my understanding is that the drugs used for kids, a lot of it is unlabeled and it is very, very high.

Mr. SCHULTZ. We've seen those numbers and we don't have a basis to question them. We don't know. We can't affirm them, but we don't have inconsistent data.

Mr. SHAYS. I am going to accept that the basic argument is you are not necessarily disputing that number.

Dr. FRIEDMAN. The problem is the typical analysis——

Mr. SHAYS. Let me just tell you that the challenge we have—and I am sorry to interrupt you—we really wanted you to come third. And we are happy to have you be second, but the reason we wanted to have you third is that we have testimony from witnesses that will follow you that will make basically that claim and, therefore, it would be good. That is why we are now trying to have to adjust the question based on something we haven't had on the record.

OK, so we'll get it on the record you are not necessarily disputing it but you don't have anything that affirms it.

Dr. FRIEDMAN. That's right.

Mr. SHAYS. And we will let others testify. I'm sorry, I did interrupt you.

Mr. SCHULTZ. I was going to say, typically, under our statute, when a company comes in, it comes in to have a drug approved for a particular use, and it chooses what use it wants. That use could be for a disease and it can be for a disease population.

The question that you are raising is whether we require the company to add a new component to that application? I want to tell you that we are looking very hard at that. It is not easy, but it is certainly something that needs to be looked at.

Dr. FRIEDMAN. There are a variety of special populations—women, the elderly, other populations—to whom these questions have been asked.

Can I spend just 30 seconds in case? You probably are fully aware of this but in case you are not, the steps the agency has gone to in offering guidance for getting pediatric labeling to simplify——

Mr. SHAYS. I have no awareness, so you can have a comfort level that this will be helpful information.

Dr. FRIEDMAN. I think it will because it is one thing to say that there is a substantial off-label use in pediatric. It would be different to say has the agency done anything to try and remedy that situation.

And I can let Dr. Woodcock or Dr. Lumpkin speak to it in greater detail, but suffice it to say what this guidance does is to indicate that when a body of information exists in adult patients, that relatively little information is needed in children, perhaps only pharmacologic information to say do children metabolize the drug differently or do they have different toxicities or do you use it in different dosage form.

So, it may be quite a limited data set. You don't have to recreate all the studies that were used to get the first approval. You might have dozens or hundreds or thousands of patients in the first approval. You might have a much, much smaller number in the pediatric supplemental labeling.

Dr. Woodcock or others can speak more to that, but I just wanted to give you that.

Mr. SHAYS. I make an assumption, though, that a child growing up is a lot different than an adult.

Dr. FRIEDMAN. For some drugs that is true; for some it is not. But it's not a bad assumption.

Mr. SHAYS. OK; that was a very gracious comment.

Dr. FRIEDMAN. I guess there is no such thing as a bad assumption by the chairman, so it is probably unnecessary.

Mr. SHAYS. OK, thank you. Do you want to make a comment?

Dr. WOODCOCK. Sure. Actually, we made that assumption for a long time because it is a rational assumption, and separate trials of efficacy in children were required to get pediatric labeling on the label.

But what we have determined in consultation with all the pediatricians is that, for many diseases, the disease in children is the same disease in adults, and what you really need is childhood dosage information and childhood safety information.

So for many diseases, we don't require formal trials of the effectiveness in children. What we want is directions for pediatricians to use that drug safely at the right dose in the children, and we basically can extrapolate that it works.

So we have been working very closely with sponsors who are now in drug development to try and bring this into effect. And we work with them at each phase of their clinical trials and ask them when are you going to start studying children. You know, are you ready to go? Where is your pediatric development program?

Dr. FRIEDMAN. But for those drugs that are off-patent or those where generics exist, you understand the economic disincentive.

Mr. SHAYS. Sure. And because of that, it may be that the way we deal with secondary uses is a logical response to the challenge of bringing a drug into the marketplace. I mean, that seems to be the only hope for some who have particularly rare diseases.

You were looking like you were about to say something. My last question really involves the issue of the Orphan Products Board. My understanding is it hasn't met since—and when I use orphan products, these are rare disease issues.

Mr. SCHULTZ. Yes, sir.

Mr. SHAYS. It hasn't met since December 1994. I don't know if you have knowledge of that. And, if so, is there an explanation of why that might be the case? And I don't even know how significant it is, but I want it for the record.

Dr. FRIEDMAN. I do not have an explanation for the interim meeting that hasn't been held. I can tell you that there is planning underway for the meeting to occur this winter.

Mr. SHAYS. But, I mean, that's not 1995 and 1996, so it's a 2-year lapse. Our understanding is it hasn't met all of 1995 at all and during 1996.

Dr. FRIEDMAN. And it's going to be meeting this winter—I'm sorry, before the end of the year.

Mr. SHAYS. But that's about a 24-month gap. Does that just say to us that it's not a very important board?

Dr. FRIEDMAN. I would like to be able to get you a better answer for that. I don't have a good enough answer.

Mr. SHAYS. You all have been very helpful. We do have another panel and Mr. Towns is going to be pursuing some questions.

I have a meeting that I am going to go to. I missed half of it and I am just going to try to get to part of it, so I am going to miss

your response to Mr. Towns. He is then going to call on the next panel and I am going to get back.

I don't expect everyone from the FDA staying, but I would like someone who could respond to comments that are made. This is not to position the FDA versus someone else. It is just to get clarification and help us understand where we are going. We are just touching our toes in the water this first hearing.

Dr. FRIEDMAN. This is of sufficient importance to me that I certainly will be staying, sir.

Mr. SHAYS. I thank you for doing that. And it may be that we will just invite you to come back afterwards if you want to make an observation. It may be we won't have a question and that is why.

Dr. FRIEDMAN. I am going to stay under any circumstances. Thank you.

Mr. SHAYS. That's very nice. Mr. Towns has the floor and also is in charge for a bit of time, and I'll be back.

Mr. TOWNS [presiding]. Thank you very much, Mr. Chairman. Let me begin by saying that I agree with your testimony that if drug companies can promote off-label drugs, the potential exists that they would be less inclined to conduct or fund the required scientific research to insure drug efficacy for new use.

Can you give circumstances where a manufacturer may seek to avoid FDA review? Could you give sort of specific situations you feel that might happen?

Mr. SCHULTZ. I can. One would be if there is an off-label use and there is fairly preliminary data, maybe articles that have preliminary data, but doctors are using the drug widely. It may not be in the company's interest to do the full studies to find out whether it works or not because there is a possibility that the study will show it does not work. And so the company, under the current system, is better off just leaving things as they are.

Mr. TOWNS. Do you want to add anything else to that?

Dr. FRIEDMAN. I think it is always a matter of balance and that companies are very, very frequently well-intentioned. They are interested in promoting their products for the proper uses. And it is a matter of the balance between incentives and disincentives. And our goal is to try and help identify those factors which tip the scale so that the company will want to pursue that research or to pursue that application. And we can help in that regard.

Mr. TOWNS. How do you respond to the concerns that the cost of pursuing FDA approval for supplements uses actually generally outweigh the anticipated revenue?

Dr. FRIEDMAN. Well, I think there are some situations in which that is true. I do think, and in our working group we have identified a number of areas, one of which is oncology, where there are many instances in which we may be able to have a simpler, less cumbersome, application process that would necessarily cost less that companies would see as not such a great disincentive, even if the use should be small.

I am not saying that this can always be done in all situations, but we do think there are many situations. And people have mentioned paper applications as being at least part of the application process. We think there are ways in which we can help to simplify

and make less expensive that process, again as another way of tipping the scales in that direction.

Mr. TOWNS. What financial incentives to pharmaceutical manufacturers currently receive to meet the FDA requirements for approval of supplemental applications? Do they receive any at this point?

Mr. SCHULTZ. These aren't actual dollars but the main incentive is that if they get approval of a use through the supplement process, they can put it on the label and they can promote the drug for that use. That is the big financial incentive. In addition, for orphan drugs, a specific category of drugs, there are some tax credits and grants that are available.

Dr. FRIEDMAN. And exclusivity.

Mr. SCHULTZ. Exclusivity is available for orphan drugs. Also, and this hasn't been totally successful, but for supplements there is, even if the patent is expired, a 3-year exclusivity where the company can have a 3-year right solely to do the labeling and advertising for that new use. The problem is if the patent is expired, a generic drug or another drug can be prescribed for the use even though it wouldn't be labeled.

Mr. TOWNS. Now, most off-labels do require FDA approval?

Mr. SCHULTZ. If the company wants to promote the drug for a use, it has to have FDA approval. But as long as a drug is approved for the first use, a doctor is free to prescribe it for another use based on his or her opinion, based on journal articles or whatever, without FDA approval.

Mr. TOWNS. Let me ask this and sort of reverse roles here. What can Congress do to continue to facilitate your efforts to improve drug approval rates? What can we do on this side?

Dr. FRIEDMAN. Let me start, if I may. I think as we look at this there are three areas that one can divide the responsibilities up in. One are those areas in which the Food and Drug Administration has the authority and the responsibility, and we think that we must work very hard to improve our own systems to make it simpler, more clear, more efficient, and to work with other constituencies. That is something that we can control and we can do, and we are working on that very hard right now.

There is a second area in which we don't have the full authority or responsibility, but we can sort of help move the system along. And a third area, obviously, or that component that we don't have any responsibility for or any authority and where Congress or other bodies has a real role to play. I think that identifying the economic and the patent incentives and disincentives that currently exist for pharmaceutical companies for other parts of even the reimbursement industry may be a very relevant role for congressional inquiry and, perhaps, remedy.

We don't have specific solutions that we would offer in that regard, but we think those are complicated areas. They are sensitive areas, and they are areas where the pharmaceutical industry might really benefit or see additional benefits from some remedies that you all could think about. I think that would be my simple answer.

Mr. SCHULTZ. I just want to add one thing. I think probably the biggest reason that the story we have to tell about drug approvals, and to some extent supplements, is the Prescription Drug User Fee

Act that Congress passed in 1992. That act will expire next year and there is broad support for it by the agency and by the industry, and I think by consumers. It has been successful beyond anybody's dreams. I think in that process there will be discussion about whether the goals for reviewing supplements should be brought down.

But that is a very important contribution that Congress made and we are going to need to ask for your help in renewing it.

Mr. TOWNS. Thank you.

Dr. FRIEDMAN. That is an absolutely excellent point.

Mr. TOWNS. Do you have anything you want to add? You don't have anything you want to tell us to do? Let me thank all three of you for your testimony. We certainly appreciate it. And, of course, you have been extremely helpful. Thank you.

Dr. FRIEDMAN. Thank you.

[The letter referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 14 1996

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Reform and Oversight
House of Representatives
Washington, D.C. 20515-6148

Dear Chairman Shays:

This is in follow-up to your September 12, 1996 hearing on "Off-Label Drug Use and Food and Drug Administration (FDA) Review of Supplemental New Drug Applications (SNDAs)." You had asked about the Orphan Products Board meetings. We have scheduled a meeting for this fall and will continue to hold meetings at least once a year as required by the Board's charter.

The Orphan Products Board last met in December 1994. Its last Public Meeting was held in June 1994. The 1994 Public Meeting was attended by only five non-Government individuals, representing groups with which Board members already met frequently. At that time, the Board's coordination and information exchange functions were proceeding very smoothly without the need for routine formal meetings. Given the lack of public interest in the Board meetings, it was agreed that FDA and Office of the Assistant Secretary of Health (OASH) staff would arrange to call future meetings at such times as they were needed.

Since our last Board meeting, FDA, the National Institutes of Health (NIH), and the Centers for Disease Control (CDC) personnel involved with orphan products issues have been in nearly constant contact on issues of mutual concern. Topics included development of the rare disease database at NIH, research funding priorities, product availability, grant review methods, and numerous other subjects. Other Board members, including the Department of Defense representative, have been consulted as needed on important issues where that agency was involved, including collaborative development of botulinum toxin products.

The promotion of orphan product development has continued, our designation and grant programs are working extremely well, and more and more products are reaching the market. As previously mentioned, collaboration among the Federal agencies has continued without interruption, where and when most needed.

FDA has conducted additional outreach activities with other Federal and non-Federal programs in support of orphan product development.

Information about the orphan products program is widely accessible across agencies, as well as to professional and public audiences through a variety of publications and, recently, the Internet.

We hope this information is helpful. If we may be of any further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: The Honorable Edolphus Towns
Ranking Minority Member
Subcommittee on Human Resources
and Intergovernmental Relations

Mr. TOWNS. Let me call up our next panel. Dr. Runowicz, Dr. Kauffman, Abbey Meyers and Dr. William Kennedy, please come forward. We always swear in all of our witnesses, even Members of Congress.

[Witnesses sworn.]

Mr. TOWNS. Thank you. Let the record reflect that they all answered in the affirmative. Why don't I begin with you, Dr. Runowicz. I understand that you have a scheduling problem.

STATEMENTS OF CAROLYN RUNOWICZ, AMERICAN SOCIETY OF CLINICAL ONCOLOGY; RALPH KAUFFMAN, AMERICAN ACADEMY OF PEDIATRICS; ABBEY MEYERS, PRESIDENT, NATIONAL ORGANIZATION FOR RARE DISEASES; AND WILLIAM KENNEDY, PHARMACEUTICAL AND RESEARCH MANUFACTURERS OF AMERICA

Dr. RUNOWICZ. Thank you, Mr. Towns. I am Dr. Carolyn Runowicz. I am here today on behalf of the American Society of Clinical Oncology. With more than 10,000 members, ASCO is the national medical specialty society for cancer physicians and physician researchers. I am also representing the Society of Gynecologic Oncologists, with approximately 800 physician members who administer comprehensive cancer care for women.

As a board-certified specialist in gynecologic oncology, I treat women with cancer, primarily cancer of the ovary or other gynecologic tumors. As a survivor of breast cancer, I also know personally the disease and the perspective of the patient. I am pleased to address the subcommittee today in both capacities concerning the topic of off-label usage of FDA approved drugs. There may be no other therapeutic area in which FDA approved drugs are used more extensively in ways other than those set forth in FDA approved labeling. In light of the fact that most anti-cancer therapy involves a combination of drugs not referenced on labels, almost all cancer patients treated with drugs will receive off-label treatment.

Over the past two decades, a number of new anti-cancer agents have been introduced. Because of these and other advances in cancer therapy, many cancers are now curable. These include a significant percentage of childhood leukemias, Hodgkin disease and testicular cancers. For the most commonly occurring cancers—prostate, breast, lung and colo-rectal—progress is less substantial but, nonetheless, measurable.

Progress in cancer treatment occurs rapidly but incrementally, often in small steps that make a difference in survival or quality of life. New products are always welcome and the FDA is doing a much better job than in the past to make therapeutic advances in the form of new products available to the American people as quickly as possible. FDA has responded to many of the demands of an increasingly vocal and effective cancer patient advocacy movement. The agency now seems to give pending new drug approvals for cancer the same priority that is given to AIDS therapies and that should be accorded to products for any life-threatening disease.

In cancer, however, new drug approvals are only the beginning of the story. Much of the incremental progress in cancer treatment requires finding new uses for already approved drugs. Moreover,

our most effective chemotherapy regimens are combinations of two or more approved drugs.

Combination chemotherapy regimens are not usually reviewed or approved by FDA and, thus, do not routinely appear on product labeling. In addition, for a variety of reasons, FDA-approved labeling almost never keeps up with new uses of products. As a result, there is a substantial disconnect between the FDA label and the actual practice of cancer medicine.

For virtually every anti-cancer drug, appropriate medical usage differs from the terms of the product labeling.

Consider cisplatin, a mainstay of modern chemotherapy. It is approved for treatment of bladder, ovarian, and testicular cancer. But over the last decade, it has been found useful in 10 or more other distinct tumors, including breast, cervical, endometrial, lung, and prostate cancer, none of which is reflected in the cisplatin labeling. Cisplatin is also most effective in combination with other drugs, but these combination regimens are generally not noted in the label.

A newer product that is being developed in a similar fashion is Taxol, which was originally approved in 1992 for treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy. Very quickly, Taxol became part of the standard primary treatment of ovarian cancer where, combined with cisplatin or a related drug, it has improved response rates and extended survival as off-label. I have brought a copy of the published research, a New England Journal of Medicine article by McGuire establishing Taxol as primary therapy off-label.

Taxol is now widely used to treat breast, bladder, esophageal, head and neck and lung cancer, but its labeling reflects approval only for second-line treatment of ovarian cancer, the original approval, and for treatment of breast cancer after failure of first-line therapy.

Oncologists are well aware of the inadequacies of the FDA-approved label as a guide to treatment and they adapt their practice accordingly. Instead of relying on drug labeling for the requisite data, we look to peer-reviewed medical journals that report the results of many ongoing clinical trials that are constantly refining quality cancer care through new uses of approved drugs. Oncologists also rely on continuing medical educational programs, medical textbooks, and other reliable sources to keep current with quickly evolving cancer therapies.

Recognizing the possibly special circumstances of cancer drug development, the American Society of Clinical Oncology [ASCO] has proposed a method for expediting the supplemental new drug application, or SNDA, at least for cancer drugs. ASCO has suggested to FDA that it should permit pharmaceutical sponsors to use reports of clinical trials and peer-reviewed medical journals as the basis for SNDA approvals. These so-called literature-based SNDA's, or paper SNDA's, are authorized under current FDA law but are not routinely utilized. ASCO believes that SNDA's would be more widely pursued if FDA were receptive to reports in the peer-reviewed literature as a basis for approval without insisting on reviewing the raw data underlying those reports, which is generally perceived as the agency's current policy.

However, even if the SNDA process is made more efficient by FDA, it still will not be possible to keep pace with rapid developments in cancer research. For this reason, ASCO has also urged FDA to relax its restrictions on dissemination, not promotion, of reliable medical information by pharmaceutical sponsors. Among the types of information that we believe are generally reliable are peer-reviewed medical journals, standard medical textbooks, and independently conducted educational seminars. In the academic research environment in which I practice, obtaining the latest data on new treatments is not usually a problem; however, our colleagues in non-academic practice settings around the country may be less likely to have easy and timely access to this potentially life-extending information. Oncologists are trained to review such information with a critical eye and we believe the risk that they will be misled by independently derived medical data is much less than the risk that they will not have access to it as quickly as possible for the benefit of the patient. In general then, ASCO supports regulatory policies that optimize the flow of peer-reviewed, high quality, reliable medical information.

We note that most patient advocacy groups in the cancer community have positions that are consistent with ASCO's policies, including the National Coalition for Cancer Survivorship and various breast and prostate support groups, as well as the American Cancer Society. From my own experience as a patient, I can attest to the intense desire of patients with cancer to have access to as much information as quickly as possible. Knowing how much new information about cancer therapy is developed on a daily basis, I would not be content with data that may have been accurate a year ago and is perhaps obsolete now.

Cancer may very well be a special case requiring special regulation from FDA. None of the proposals advocated by ASCO and supported by the patients require legislation; thus, FDA, if it were so inclined, could act immediately to expedite SNDA's by greater reliance on published reports and to lift restrictions on the dissemination of reliable medical information. Both patients with cancer and the physicians who treat them would benefit from such action.

Thank you.

[The prepared statement of Dr. Runowicz follows:]

Mr. Chairman, I am Dr. Carolyn Runowicz. I am here today on behalf of the American Society of Clinical Oncology (or ASCO). With more than 10,000 members, ASCO is the national medical specialty society for cancer physicians and physician researchers. I am also representing the Society of Gynecologic Oncologists.

As a board-certified specialist in gynecologic oncology, I treat women with cancer, primarily cancer of the ovary or other gynecologic tumors. As a survivor of breast cancer, I also know the disease from the perspective of a patient. I am pleased to address the Subcommittee today in both capacities concerning the topic of off-label usage of FDA-approved drugs. There may be no other therapeutic area in which FDA-approved drugs are used more extensively in ways other than those set forth in FDA-approved labeling. In light of the fact that most anticancer therapy involves combinations of drugs not referenced on labels, almost all cancer patients treated with drugs will receive off-label treatment.

Over the past two decades, a number of new anticancer agents have been introduced. Because of these and other advances in cancer therapy, many cancers are now considered curable. These include a significant percentage of childhood leukemias, Hodgkin's disease and testicular cancers. For the most commonly occurring cancers - - prostate, breast, lung and colorectal - - progress is less substantial but nonetheless measurable.

Progress in cancer treatment occurs rapidly but incrementally, often in small steps that make a difference in survival or at least in quality of life. New products are always welcome, and the Food and Drug Administration (FDA) is doing a much better job than in the past to make therapeutic advances in the form of new products available to the American people as quickly as possible. FDA has responded to many of the demands of an increasingly vocal and effective cancer patient advocacy movement. The agency now seems to give pending new drug approvals for cancer the same priority that is given to AIDS therapies and that should be accorded to products for any life-threatening disease.

In cancer, however, new drug approvals are only the beginning of the story. Much of the incremental progress in cancer treatment requires finding new uses for already approved drugs. Moreover, our most effective chemotherapy regimens are combinations of two or more approved drugs.

Combination chemotherapy regimens are not usually reviewed or approved by FDA and thus do not routinely appear on product labeling. In addition, for a variety of reasons, FDA-approved labeling almost never keeps up with new uses of products. As a result, there is a substantial disconnect between the FDA label and the actual practice of cancer medicine.

For virtually every anticancer drug, appropriate medical usage differs from the terms of the product labeling. Consider cisplatin, a mainstay of modern chemotherapy. It is approved for treatment of bladder, ovarian and testicular cancer, but over the last decade it has been found useful in ten or more other distinct tumors--including breast, cervical, endometrial, lung and prostate cancer--none of which is reflected in the cisplatin labeling. Cisplatin is also most effective in combination with other drugs, but those combination regimens are generally not noted in the label.

A newer product that is being developed in a similar fashion is Taxol, which was originally approved in 1992 for treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy. Very quickly, Taxol became part of the standard primary treatment of ovarian cancer, where, combined with cisplatin or a related drug, it has improved response rates and extended survival. Taxol is now widely used to treat breast, bladder, esophageal, head and neck, and lung cancer, but its labeling reflects approval only for second-line treatment of ovarian cancer (the original approval) and for treatment of breast cancer after failure of first-line therapy.

Oncologists are well aware of the inadequacies of the FDA-approved label as a guide to treatment, and they adapt their practice accordingly. Instead of relying on the drug labeling for the requisite data, we look to peer-reviewed medical

journals that report the results of the many ongoing clinical trials that are constantly refining quality cancer care through new uses of approved drugs. Oncologists also rely on continuing medical education programs, medical textbooks and other reliable sources to keep current with quickly evolving cancer therapies.

Recognizing the possibly special circumstances of cancer drug development, the American Society of Clinical Oncology has proposed a method for expediting the supplemental new drug application (or SNDA) process, at least for anticancer drugs. ASCO has suggested to FDA that it should permit pharmaceutical sponsors to use reports of clinical trials in peer-reviewed medical journals as the basis for SNDA approvals. These so-called literature-based SNDA's (also known as "paper" SNDA's) are authorized under current FDA law but are not routinely utilized. ASCO believes that SNDA's would be more widely pursued if FDA were receptive to reports in the peer-reviewed literature as a basis for approval without insisting on review of the raw data underlying those reports, which is generally perceived as the agency's current policy.

However, even if the SNDA process is made more efficient by FDA, it still will not be possible to keep pace with rapid developments in cancer research. For this reason, ASCO has also urged FDA to relax its restrictions on dissemination of reliable medical information by pharmaceutical sponsors. Among the types of information that we believe are generally reliable are peer-reviewed medical

journals, standard medical textbooks and independently conducted educational seminars. In the academic research environment in which I practice, obtaining the latest data on new treatments is not usually a problem. Our colleagues in nonacademic practice settings around the country may be less likely to have easy and timely access to this potentially life-extending information. Oncologists are trained to review such information with a critical eye, and we believe the risk that they will be misled by independently derived medical data is much less than the risk that they will not have access to it as quickly as possible for the benefit of their patients. In general, then, ASCO supports regulatory policies that optimize the flow of peer-reviewed, high quality, reliable medical information.

We note that most patient advocacy groups in the cancer community have positions that are consistent with ASCO's on these issues, including the National Coalition for Cancer Survivorship and various breast and prostate support groups as well as the American Cancer Society. From my own experience as a patient, I can attest to the intense desire of people with cancer to have access to as much information as possible as quickly as possible. Knowing how much new information about cancer therapy is being developed on a daily basis, I could not be content with data that were accurate and up-to-date as of last year but perhaps obsolete now.

Cancer may very well be a special case requiring special regulation from FDA. None of the proposals advocated by ASCO and supported by the patients requires legislation. Thus, FDA could, if it were so inclined, act immediately to expedite SNDA's by greater reliance on published reports and to lift restrictions on dissemination of reliable medical information. Both people with cancer and the physicians who treat them would benefit from such action.

Mr. TOWNS. Thank you. Dr. Kauffman.

Dr. KAUFFMAN. Thank you, Mr. Towns. I am Dr. Ralph Kauffman, professor of Pediatrics and Pharmacology at the University of Missouri and director of Medical Research at the Childrens Mercy Hospital in Kansas City.

I am pleased for the opportunity to be here this morning on behalf of the American Academy of Pediatrics. This is an organization representing 50,000 pediatricians dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. I should also mention I have spent 16 years as a member of the academy's committee on drugs, including 4 years as chairman of that committee.

A critical issue for pediatricians, as you have heard this morning, over the past 30 years has been the lack of approval and labeling of medications for use by infants, children and adolescents.

The question was asked from the previous panel, and I can give you some numbers today. It is shocking that only 20 percent of all drugs marketed in the United States have been labeled for use by children. This is based on a survey of marketed drugs in 1977. The survey was repeated in 1991, and nothing changed in that 20-year period.

Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer that they are not approved for use by children. A related problem that needs to be acknowledged is a lack of dosage formulations which can be used in children, particularly infants and smaller children.

Let me give you an example. Asthma was mentioned by one of the previous speakers this morning. This is the most common chronic illness affecting several million children in the United States today. It is so common that it is the most common reason for hospital admission of children. Undoubtedly, many of you have, or virtually all of you, have family members or friends who suffer from asthma.

Albuterol, one of the drugs most frequently used to treat asthma, must be prescribed off-label for children because the form of the drug necessary to provide breathing treatments, the most effective way of administering this drug, is labeled, "Safety and effectiveness have not been established in children under 12 years of age."

The Kefauver-Harris amendments of 1962 were mentioned earlier. These were amendments to the Food and Drug Act that provided that drugs be demonstrated by well-controlled studies to be effective for their intended uses, as well as safe. While this provision has been applied to the approval of drugs for adult use, it has not been extended to use by children in the labeling of a majority of drugs. Fully 25 percent of the population of the United States has been disenfranchised from this statute.

This is particularly ironic since passage of the Federal Food, Drug, and Cosmetic Act of 1938 and later in 1962 the Kefauver amendments. Both of these were passed in the aftermath of therapeutic catastrophes involving administering drugs to children based on adult information.

Absence of studies to support labeling of the majority of drugs for children places a physician in the untenable position of either prescribing without adequate labeling or denying the pediatric patient

access to important therapeutic agents. When confronted with this dilemma, the physician invariably prescribes the medication off-label. As a result, off-label use of medications has, by default, become established standard of care for children in the United States.

It is important to emphasize that off-label prescribing is neither illegal nor improper; however, from the patient's perspective, infants and children frequently are exposed to medications without the benefit of adequate studies to document safety and efficacy or to establish doses appropriate for their age.

Last week I was asked to see in consultation a 1-month-old infant with a life-threatening infection which was resistant to all antibiotics except one. The single antibiotic to which this infection was sensitive is not labeled for children, much less 1-month-old infants.

We had to administer this medication to the infant with no information regarding appropriate dose for this age patient or specific information regarding possible side effects. Under the circumstances, we did the only thing we could, combining our knowledge of the physiology of an ill 1-month-old infant with knowledge of how the drug is given to adults.

Fortunately, in this particular case, the infant improved and is currently recovering; however, the outcome of this type of scenario, which is repeated throughout the United States on a daily basis, is not always so favorable.

Despite various attempts by the Food and Drug Administration, which you have heard this morning, to address this problem, the proportion of approved new drugs labeled for children has not changed during the past decade.

An academy review of the 28 new drugs approved by the FDA in 1995 indicated that only 4 were approved with pediatric labeling. The sponsors of 10 of these drugs have indicated pediatric studies are in progress or will be done in the future, and sponsors of the remaining 14 drugs have indicated studies are not needed since, in their judgment, the drugs are unlikely to be used in children. However, looking at that list, we know that several of these 14 drugs undoubtedly will be used in children.

While we commend the recent efforts of the FDA to encourage the inclusion of pediatric data in FDA approved labeling, progress to date has been modest and sporadic. Because of that, the American Academy of Pediatrics believes additional steps must be taken to augment the FDA initiatives, and we have some very specific recommendations to make.

First of all, we have been told consistently over the past 20 years that the FDA does not have regulatory authority under the current statute to require pediatric studies. They can request them, they can encourage them, they can facilitate them to the extent they are able, but they cannot require them.

Because of that, we recommend that Congress provide FDA with specific statutory authority and responsibility to make studies in appropriate pediatric populations a requirement during clinical trials of each new drug which has anticipated use in children, unless it is determined by an independent panel of experts in pediatric medicine that there is no anticipated use of that drug in children.

Second, we recommend that Congress establish an independent panel of experts in pediatric medicine composed of experts from, for example, the Academy of Pediatrics, Pediatric Pharmacology Research Unit Network, the U.S. Pharmacopeia, as well as other experts in pediatrics with authority to advise the FDA which new drugs would have pediatric applications and the types of studies required in specific populations; to determine the need for studies of specific marketed drugs in the pediatric population; and, advise the FDA on the approvability of specific NDA's for pediatric indications.

Third, we recommend that FDA establish age definitions for children to be used for regulatory purposes as a standard throughout the agency.

Fourth, the FDA, we feel should, in consultation with an independent panel of experts in pediatric medicine, develop, prioritize, and publish from the compendium of already approved patented and off-patent drugs a list of drugs for which pediatric labeling is necessary.

We would like to see the FDA authorized to fund studies required to accomplish pediatric labeling of off-patent drugs because there is absolutely no economic incentive for a private sponsor to do studies to support labeling in off-patented drugs. Somehow, this needs to be done because a number of drugs that are off-patent are still not labeled for children and are used on a regular basis.

We recommend the FDA develop guidelines for the inclusion of pregnant and/or lactating women in clinical trials of new drugs and request such studies be performed when there is a high probability the drug will be used in these populations.

And, last, the academy supports consideration of proposals to provide economic incentives to companies who conduct pediatric studies and who provide pediatric dosage formulations for new drugs as well as already approved drugs. Consideration should be given to patent extension for companies who complete pediatric studies which lead to pediatric labeling.

Thank you, Mr. Towns, for the opportunity to present this important health care issue to the committee. I have submitted a more detailed written statement of my testimony for the record and I would be happy to answer questions.

Mr. TOWNS. Your entire statement will be included in the record. Let me just say to all of you it will.

[The prepared statement of Dr. Kauffman follows:]

Good Morning. I am Ralph Kauffman, MD, Professor of Pediatrics and Pharmacology at the University of Missouri, Kansas City and Director of Medical Research at the Children's Mercy Hospital in Kansas City, Missouri. I am pleased to be here this morning on behalf of the American Academy of Pediatrics, an organization representing 50,000 pediatricians dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. I spent 16 years as either a member of or consultant to the American Academy of Pediatrics Committee on Drugs, including four years as Chairman. I should also add that I currently serve as a member of the Pediatric Advisory Committee of the US Pharmacopoeia. I have devoted virtually my entire professional career to the development of medications for the safe and effective treatment of diseases affecting infants and children.

A critical issue and a high priority of pediatricians for the past 30 years has been the approval and labeling of medications for use by infants, children and adolescents. It is shocking to note that few drugs -- only approximately 20 percent of all drugs marketed in the United States -- have been labeled for use by infants and children. Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer in the labeling that they are not approved for use by children.

Approval of a drug for human use requires proof of efficacy and safety for its specific intended use in human beings established by well controlled clinical trials. Once approved for specific indications, the drug is labeled for interstate commerce. The labeling contains the approved prescribing information including indications, contraindications, precautions, warnings, adverse reactions, and dosage recommendations.

The Kefauver-Harris amendments to the Food and Drug Act passed in 1962 require that drugs be demonstrated by well-controlled studies to be effective for their intended uses as well as safe. While this provision has been applied to approval of drugs for use by adult patients it has not been extended to use by infants and children in the labeling of a majority of drugs. This is particularly ironic since several key Food and Drug statutes were passed in the aftermath of therapeutic catastrophes involving children. The tragic deaths of 107 children from ingestion of elixir of sulfanilamide brought about the passage of the Federal Food, Drug and Cosmetic Act of 1938, and later the tragic malformations of infants caused by maternal use of thalidomide during pregnancy led to the 1962 Kefauver amendments to the Act.

Lack of pediatric labeling does not mean that the drugs are necessarily harmful, ineffective, or contraindicated in children but simply that the clinical trials which satisfy the FDA requirements for labeling were not conducted in children. Because of this, children have not shared in therapeutic advances to the extent adult patients have nor have they been provided the same protections afforded adult patients under the 1962 Kefauver-Harris amendments to the Food and Drug statutes. Though there has been modest progress in the labeling of marketed drugs for pediatric use, it remains sporadic and incompletely addressed.

Many reasons have been advanced for not studying and labeling drugs for use by children and adolescents, but the leading issues are regulatory impediments, economic disincentives, and

reluctance on the part of the FDA to make studies in children a requirement for a new drug unless the primary use of the drug will be in children. With the exception of antibiotics, medications for fever, vaccines, and a few other therapeutic categories, pediatric use represents a relatively small segment of the total market for a drug. Companies frequently are reluctant to expend the additional time and resources to do pediatric studies with little promise of additional market potential.

CHILDREN ARE NOT SIMPLY SMALL ADULTS

It is important to understand why drugs must be studied in children to establish their safe and effective use in children. In other words, why can't studies in adults provide sufficient information for use of a drug in children? No animal model or study in adults adequately predicts the effect of drugs on children of various ages and stages of development. The dynamics of growth and maturation of various organs, the changes in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes result in significant differences between children and adults. As a result, the elimination of drugs from a child's system, the dosage required and the safety and effectiveness of a pharmacologic agent need to be studied at critical developmental stages in the pediatric population.

Even within the pediatric population there is great diversity. There may be a need to study the same drug in several pediatric groups (i.e., neonates, infants, young children and adolescents) in order to determine drug efficacy, dosing, toxicity, and appropriate formulations for each subpopulation.

OFF-LABEL USES OF DRUGS IN CHILDREN AND ADOLESCENTS

An off-label use, also known as an "unapproved" use of an approved drug, refers to a use that is not included or that is disclaimed in the approved labeling. It is important to emphasize that "unapproved use" or "off-label" use does not imply an improper or illegal use. Indeed, this off-label use may represent the only, or best, treatment available for a specific illness in a child.

As mentioned, only a minority of currently marketed drugs have undergone pediatric clinical trials and have approved labeling for use in children. These include common antimicrobial agents, medications for fever, vaccines and some asthma and allergy medications. However, most drugs used to treat illnesses in children have never been formally tested or approved for pediatric use and lack even basic dosage recommendations for children in their labeling. These include such routinely used medications as dopamine (used to treat shock), cisapride (used to treat abnormal regurgitation of stomach contents in infants and small children), ketorolac (the only available injectable non-narcotic pain reliever), midazolam (used as a sedative and to treat convulsions), and adenosine (used to treat life threatening abnormal heart beats).and the list is much longer.

Lack of studies to support labeling of the majority of drugs for use by children places the physician caring for children in the untenable position of either prescribing without adequate labeling or denying pediatric patients access to important therapeutic agents. When confronted with this dilemma the physician invariably elects to prescribe a medication without adequate pediatric labeling. As a result, off-label use of medications has, by default, become an established standard of care for children. From the patient's perspective, infants and children frequently are exposed to

medications without the benefit of adequate studies to document safety and efficacy or establish doses appropriate for their age.

A related problem is that medications not approved for use by children are not manufactured in dosage forms which can be readily administered to children. For example, many medications are provided in capsule or tablet forms which cannot be swallowed by small children and are not available in small enough dosage increments to give the proper dose to children.

CHILDREN REMAIN THERAPEUTIC ORPHANS

In a 1994 hearing before the House Subcommittee on Health and the Environment, Sumner J. Yaffe, M.D., Director of the Center for Research for Mothers and Children at the National Institutes of Health, reported that only approximately 20 percent of all drugs marketed in the United States have had clinical trials performed in children which satisfy the FDA requirements for being labeled as safe and effective for use in infants and children. He further reported, "The FDA has suggested that of the 80 drugs most frequently used to treat newborns and infants in U.S. hospitals, only five are labeled for use by children. This does not imply that 80 percent of our drugs are contraindicated, unsafe, or disapproved for use in infants and children. Rather, it means that necessary testing has not been done to produce the data that would enable the Food and Drug Administration to grant approval status for specific clinical indications and uses in pediatric populations[1]."

Drugs which need to be labeled for pediatric use may be divided into 3 categories based on their position in the approval process and market place: 1) new drugs in clinical trials, not yet approved for general marketing; 2)drugs approved for adult use but not labeled for children and still under patent protection; and 3) drugs labeled for adult but not pediatric use which are off-patent and may be marketed as generic products by multiple companies. There is at least some potential economic incentive to include pediatric clinical trials in the premarketing development of new drugs. However, once a drug is marketed for an adult indication, the economic incentive to do additional studies to include pediatric labeling is markedly reduced because the drug may be prescribed off label. In the case of drugs which are off patent, there is absolutely no economic incentive to invest in studies to expand labeling because a single sponsor can no longer benefit from such an investment due to lack of exclusivity protection of the drug.

An examination of new molecular entities, which represent the most innovative new medications, approved by the FDA from 1984 through 1995 showed that approximately 80% of these medications were approved without labeling for children, although many of them are widely used to treat illness in children. An AAP survey of the 28 new drugs approved by the FDA in 1995, indicated that only four have pediatric labeling. The sponsors of 10 have indicated pediatric studies are in progress or will done in the future, and sponsors of the remaining 14 drugs have indicated studies are not needed, since it is not likely that those drugs will be used in children. However, several of these 14 drugs undoubtedly will be used in children. For example, the sponsor of dirithromycin, a new macrolide

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[1]Statement by Summer Y. Jaffe, MD, Director, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, National Institute of Health, before the Subcommittee on Health and the Environment, House Committee on Energy and Commerce. February 8, 1994.

antibiotic approved in 1995, has indicated a pediatric study is not needed or planned although it is highly likely this antibiotic will be used by physicians to treat infections in children as well as adults.

LACK OF LABELING FOR USE OF DRUGS DURING PREGNANCY AND LACTATION

Two other disenfranchised populations of patients with respect to drug labeling are women who are pregnant and those who are breast feeding their infants. Pregnant and lactating women are routinely excluded from clinical trials of new drugs. Consequently, the labeling for very few drugs includes definitive information on or an assessment of risks associated with maternal use of the drug. This impacts the health of children because of the unknown risk to the unborn child and the unknown effects on the nursing child when the mother uses medication.

FDA EFFORTS AT PEDIATRIC LABELING

In 1979 FDA published regulations pertaining to the specific content and format of prescription drug labeling that stipulate that pediatric labeling be based on adequate, well-controlled studies involving children. The intention of these regulations was to encourage drug labeling that would regularly provide adequate information about the use of drugs in children. However, the result was not more adequately labeled drugs; rather labels simply state that the drug's safety and effectiveness in children have not been established. Eighty percent of the prescription drugs currently marketed in the United States are labeled with such disclaimers.

In an attempt to remedy this situation the FDA published regulations on December 13, 1994, aimed at increasing pediatric information in drug labeling and facilitating addition of pediatric indications to drug labeling. The 1994 regulations recognize several methods of establishing substantial evidence to support pediatric labeling claims. These include 1) allowing inclusion of published pediatric information in the labeling and 2) approval of pediatric use based on adult efficacy studies where the disease for which the drug is to be used is substantially the same in children and adults thereby allowing pediatric studies to focus on dosing and safety data for children. The regulations respond to concerns that current prescription drug labeling too often does not contain adequate information about the uses of drugs in children and are meant to provide the physician with more complete and useful information when prescribing for children. Though the new regulations have been in effect for almost two years, it is not yet apparent that they have resulted in any increase in new drug labeling for children.

RECOMMENDATIONS:

While we commend the efforts of the FDA at internally reforming the agency, we are concerned that the regulations of December, 1994 meant to encourage the inclusion of pediatric data in FDA-approved labeling, have failed to achieve their goal. The American Academy of Pediatrics believes additional steps must be taken to augment the FDA initiatives and supports the following measures to overcome some of the principal obstacles to labeling medications for children:

- AAP recommends that Congress provide the FDA with specific statutory authority and responsibility to make studies in appropriate pediatric populations a requirement during clinical trials of each newdrug with potential use by children, unless it is determined by a panel of experts in pediatric medicine that there will be no use of that drug in children and/or adolescents.

- The Congress should establish an independent panel of experts in pediatric medicine, composed of experts from the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, U.S. Pharmacopoeia, as well as other experts in pediatric research with authority to:

  - advise FDA which new drugs would have pediatric applications and the types of studies required in specific pediatric populations;

  - determine the need for studies of specific marketed drugs in the pediatric population;

  - advise the FDA on the approvability of specific NDA's;

- FDA should establish age definitions for children to be used for regulatory purposes as the standard throughout the Agency. The AAP recommends the following age breakdown:

  - child means a neonate, infant, young child, or adolescent;

  - neonate means a child from birth to the age of one month (30 days);

  - infant means a child from the age of one month to the age of two years;

  - young child means a child from the age of two years to the age of twelve years;

  - adolescent means a child front the age of twelve to the age of eighteen years.

- The FDA should, in consultation with the independent panel of experts in pediatric medicine, develop, prioritize and publish from the compendium of already approved and patented drugs, an initial list of drugs for which pediatric labeling is necessary.

- The FDA should be authorized, in consultation with the independent panel of experts in pediatric medicine, to identify, prioritize, and publish a list of off-patent drugs for which

pediatric labeling is necessary and be authorized to fund studies required to accomplish pediatric labeling of those drugs.

- The FDA should develop guidelines for the inclusion of pregnant and/or lactating women in clinical trials of new drugs and request such studies be performed when there is a high probability the drug will be used in these populations.

- The Academy supports consideration of proposals to provide economic incentives, if necessary, to companies who conduct pediatric studies and who provide pediatric dosage formulations for new drugs as well as already approved and off-patent drugs. Consideration should be given to patent extension for companies who complete pediatric studies which lead to pediatric labeling.

The American Academy of Pediatrics is anxious to work with Members of Congress to develop the best and most far-reaching protections for infants, children, adolescents and young adults. We welcome the opportunity to continue this dialogue.

Mr. TOWNS. Thank you very much. Ms. Meyers.

Ms. MEYERS. Thank you, Mr. Towns. I am Abbey Meyers. I represent the National Organization for Rare Disorders, which is a nonprofit, voluntary health agency dedicated to the identification, treatment, and cure of rare diseases. We are a consumer group who advocated for passage of the Orphan Drug Act in 1983, and we continue to monitor its progress.

The problem with off-label uses, I think, is it is not peculiar to cancer. It is peculiar to many, many orphan indications. For example, there are about 200 different types of cancer and there are only 4 or 5 of them that do not fit the basic definition of an orphan disease. Under the law, any disease or condition affecting fewer than 200,000 Americans is an orphan disease.

So beyond breast cancer and prostate cancer and lung cancer and a couple of others, all the rest qualify for orphan drug status. Indeed, Taxol was originally developed as an orphan drug because ovarian cancer is an orphan indication, and they stepped back and relinquished that designation.

Now, the question is: Why would any company want to invest the money to get a drug approved for an off-label indication? If you have a drug like TPA which is for heart attacks and it is a very big-selling drug and you find out that there may be a market for stroke which is going to add a few hundred thousand or a few million people a year to that market, certainly it is worth developing something for that large market of people. But for small markets of people, rare diseases, there is no reason to do that. Most companies don't see any reason to do it.

And so the off-label problem is very peculiar to all rare diseases, including the cancers and including pediatric uses of many drugs, because serious pediatric illness is quite rare in children. Most children are healthy and they are going to take cough medicine and antibiotics, but they are not going to need the kinds of drugs that we are talking about unless their condition is rare.

So what we want is to find a way to get these off-label indications on the labels. There is enough evidence out there of companies promoting the use of drugs for off-label uses that didn't work. Some have been quite tragic. There are drugs that were for antiarrhythmia, to normalize heart rhythm, that actually caused heart attacks in many people. And I have cited some of those in my written testimony which is being submitted for the record.

In order to do this, who is going to fund the research? The companies don't want to fund the research. NIH says that they are in the business of basic research; they don't like to fund clinical research. And Dr. Haffner's office at the FDA has a tiny little appropriation each year of $12 million. Now, the scope of the problem is that we are talking about 5,000 rare diseases, and she has $12 million a year to fund the clinical research on new treatments for these diseases. That is just not going to fly.

Indeed, one of the drugs that I have submitted on the last page of my testimony, or the next to the last, is a drug called hydroxyurea. I have listed it as an off-label use for a very complicated disease called essential thrombocythemia. However, this drug—it is very interesting—it is on the market as a cancer drug, but about a year ago some papers were published saying that this

is the most effective drug for sickle cell anemia. This drug should probably be approved for sickle cell anemia as soon as possible. Not only isn't the company supporting the research on it for sickle cell anemia, but Dr. Haffner's office under that $12 million appropriation is supporting the clinical trials to someday get this drug approved for sickle cell anemia.

It is wrong. It is wrong that this is happening and that companies are not stepping forward, especially when there was such an excellent paper published in the New England Journal of Medicine saying that this is a very important breakthrough.

So what we think should be done is a number of things. First of all, to raise the priority of supplemental applications at FDA. Remove the gag rule, because right now if you call up FDA and ask why isn't my drug labeled for my disease, they say "we're not allowed to tell you; it's a trade secret." Well, the secrecy under which FDA operates is horrendous because even if they know the company submitted the data for that drug and they found out that the drug was unsafe or ineffective, consumers and doctors can't find out. So the agency must be allowed to talk to the public.

Require the FDA to identify these candidate drugs, create a supplemental review division that would look at these drugs individually and get them out of the divisions that are so bogged down with reviewing new NDA's.

And Congress should consider financial incentives to the industry to support these clinical trials. If they gave them a tax credit for every $1 that they invest in the clinical trials to get supplemental NDA's approved, I think there wouldn't be so much resistance to performing the research.

And, finally, drug companies must understand that they have a social responsibility to do no harm, and to know that their drugs are being prescribed off-label without being able to tell people what dose or what the side effects are is doing harm. Thank you.

[The prepared statement of Ms. Meyers follows:]

Mr. Chairman and Members of the Committee:

Thank you for inviting me to speak with you today. My name is Abbey Meyers and I am President of the National Organization for Rare Disorders (NORD), a unique federation of more than 140 non-profit voluntary health agencies dedicated to the identification, treatment and cure of rare "orphan diseases." We are the patient group that worked for the passage of the Orphan Drug Act of 1983. We continue to advocate for and monitor the development of treatments that would not be developed without the incentives of this lifesaving legislation.

Rare Diseases are "Off-Label" Diseases

This morning, I would like to address the serious problems associated with the "off-label" uses of prescription drugs for the treatment of rare "orphan" diseases. While policy-makers often recognize this problem as peculiar to cancer treatment or the pediatric uses of adult drugs, the problems of rare disorders are usually ignored. Regretfully, most people affected by these unusual diseases do not have therapies which have been approved by the Food and Drug Administration (FDA).

Since very few treatments are developed solely for these small populations of patients, a physician's armamentarium is quite often limited to drugs that were developed and marketed for more prevalent health conditions. Unfortunately, when no clinical trials are ever conducted to prove their effectiveness on rare diseases, health insurance companies often claim that such treatments remain "experimental" and, therefore, refuse to reimburse for their use. In addition, physicians concerned about liability matters may avoid prescribing such drugs even though patients may need them.

The majority of orphan diseases remain totally without any treatment; however, for those rare disorders which are to some degree "treated" with pharmaceuticals, NORD estimates that probably 90 percent must rely on "off-label" uses of drugs.

To put the problem in perspective, an "orphan disease" is defined under federal law as a disease or condition that affects fewer than 200,000 Americans. Most of these illnesses are unfamiliar to the public, as well as many medical professionals. However, some are quite well known such as cystic fibrosis (20,000 -30,000 Americans), Duchenne muscular dystrophy (10,000 Americans) and Amyotrophic Lateral Sclerosis, commonly known as Lou Gehrig's Disease (30,000 Americans). There are over 5,000 rare disorders, most of which are genetic. **Cumulatively affecting an estimated 20 million Americans, orphan diseases represent a major health problem.**

The Orphan Drug Act . . . ***Just a first step?***

Because each rare disorder affects a small number of people, pharmaceutical companies did not develop drugs to treat them until 1983 when the Orphan Drug Act became law. This federal statute assures manufacturers that they will not lose money, and will actually have a chance to make a profit, if they develop a drug for a very limited market. The law contains several financial incentives designed to entice manufacturers into this field of research and development, including tax credits and a seven-year period of exclusive marketing rights.

Since 1983, over 130 orphan drugs have been approved for marketing in the United States, and approximately 650 designated orphan drugs are in the research pipeline. This law is undoubtedly one of the most successful pieces of legislation that Congress has enacted in recent decades. Subsequently, Japan and Singapore have passed similar laws and the European Union is formulating their own orphan drug legislation right now.

The "Orphan" Dilemma

While the Orphan Drug Act spurred development of new treatments for rare diseases, it did not address the problem of "off-label" usage -- it remains very difficult to get rare diseases "on-label." There is simply little reason and no incentive for a company to study the use of a drug on a rare disease if the compound is already approved and on the market for a more prevalent and, thus, more lucrative health condition. It costs money to fund clinical trials, and manpower to submit a Supplemental

New Drug Application (SNDA). Therefore, pharmaceutical manufacturers have determined that it doesn't make sense to spend such resources unless their market will be substantially expanded by the new approval. Since the vast majority of pharmaceuticals are developed for common diseases with very large markets, few manufacturers ever submit applications to the FDA for approval of new rare indications.

The National Organization for Rare Disorders (NORD) strongly believes that physicians should continue to be permitted -- and, in some cases, even encouraged -- to prescribe drugs for illnesses that are not on the label. Although, if the disease is not listed, then physicians are not likely to know the proper dosage and possible side effects for the secondary use. **In fact, in the absence of any well-controlled clinical trials to prove the safety and effectiveness for "off-label" indications, neither patients nor their physicians can be assured that these drugs actually work and do not carry hidden dangers.**

Most rare diseases are without any treatment simply because they have not been studied enough by the medical research community and knowledge of the underlying biochemical or genetic defect that causes them is lacking; others are types of birth defects which have irreversible symptoms (e.g. mental retardation). But increasingly, scientists are beginning to understand the causes of *some* of these diseases, and their only weapons are drugs that are already commercially available. Thus, discovery of treatments for orphan diseases can be serendipitous through a "shotgun" approach of trying every drug in a class until you, hopefully, find one that works.

For example, scientists may know that a disease is caused by too much or not enough of a chemical in the brain such as dopamine, so they experiment with drugs that were designed to affect the level of dopamine (e.g. Parkinson's disease is linked to abnormally low levels of dopamine, whereas schizophrenia is characterized by too much dopamine). Every drug that affects dopamine levels may be examined and tried (the "shotgun approach"), and if a drug is found to work on some patients, a paper will be published in a medical journal. Thereafter, other doctors treating patients with the same rare disorder

will also use that drug. In time, the treatment will become standard medical therapy for that particular illness even though it has not been studied in well-controlled clinical trials and serious questions about proper dosage and side effects in a unique patient population remain unanswered.

When academic scientists want to study the drug to answer these questions, the manufacturer is usually not interested in funding the research. Furthermore, publicly funded research sponsored by the National Institutes of Health (NIH) tends to favor "basic" research rather than "clinical" research on humans. According to the ***National Commission on Orphan Diseases'*** 1989 Report to Congress, there are few other options for funding of clinical studies on rare diseases. The small amount of funds appropriated to the ***FDA's Orphan Products Grants Program*** each year to fund clinical trials on treatments for rare diseases cannot possibly address the "off-label" dilemma for 5,000 rare diseases.

To illustrate how pervasive this problem is for rare diseases, NORD reviewed just a small sample of diseases included in our ***Rare Disease Database*** (Internet address, http://www.nord-rdb.com/~orphan). We chose 25 diseases alphabetically from "A," and 25 from "T." A list of some of these diseases and their commonly prescribed drugs is attached for your perusal (Attachment A). Please note that out of 50 diseases only 14 are listed because: a) most of the 50 diseases remain totally untreatable, b) some diseases are treated with surgery and/or blood products, and c) some diseases (such as Tetralogy of Fallot) have symptoms that are controlled by drugs labeled for those *symptoms* (e.g. abnormal heart rhythm) even if the disease is not named.

An Example: **Neurological Movement Disorders and "Off-Label" Drug Use**

In addition, I asked Mitchell Brin, M.D., a leading neurologist from Mt. Sinai School of Medicine in New York City, to explain the "off-label" use of pharmaceuticals in the treatment of neurological movement disorders. Dr. Brin is the Director of the Movement Disorder Center at Mt. Sinai Medical Center. He noted that a group of movement disorders known as the ***Dystonias*** are ordinarily treated with anticholinergic drugs

approved for Parkinson's Disease, dopamine-depleting agents such as Reserpine and Tetrabenazine (antipsychotic drugs) and dopamine-blocking agents such as Haldol (haloperidol) and Orap (pimozide). While haloperidol is labeled for schizophrenia and Tourette Syndrome, and pimozide is also labeled for Tourette syndrome, both are used for a wide variety of hyperkinetic movement disorders such as myoclonus, tardive dyskinesia and the Dystonias. Moreover, clonazepam, Valium, baclofen, and carbamazine are also used for the Dystonias even though they have only been approved for other conditions.

Myoclonus, another movement disorder, is treated "off-label" with a wide variety of pharmaceutical agents ranging from anticonvulsant therapies to high blood pressure drugs, including sodium valproate, clonazepam, primidone, vigabatrin, methysergide and propranolol (Inderal). ***Tourette Syndrome*** is treated with a wide variety of drugs from antidepressants to antihypertensives and anticonvulsants that are not labeled for this condition. ***Essential tremor***, which is a common movement disorder in the elderly, is treated "off-label" with primidone and meythysergide in addition to clonazepam and alprazolam. For the rare paroxysmal dyskinesias, anticonvulsants are commonly used as well as anticholinergics and neuroleptics. Additionally, Dr. Brin points out, many of the agents used to control pain are not labeled for pain management, and some drugs commonly used to ease spasticity are not labeled for this indication.

"Off-Label" Effects on Orphan Drug Development

Why should a pharmaceutical manufacturer spend millions of dollars and several long years developing a drug for a rare disease with a limited market if another company that has spent no money on research, is allowed to make claims that their drug is effective on the same rare indication? The exclusivity provisions of the Orphan Drug Act are seriously undermined unless the FDA strictly enforces its "off-label" marketing regulations and demands proof of safety and efficacy.

The FDA and Supplemental New Drug Applications

The FDA may be aware that a drug or group of drugs has wide-ranging "off-label" uses, but their jurisdiction ends at policing promotional and marketing activities. They cannot approve a supplemental indication if no company applies for approval. Academic scientists cannot apply for changes in labeling on a drug that is proprietary to a company. In many cases, drugs that are considered standard therapy for a rare disease may be old "off-patent" drugs manufactured by several generic companies. In these instances, no company will invest funds nor manpower into seeking a supplemental approval for a drug they do not own and cannot patent. Even when a company can get a "use patent" for the new indication, when a patient fills a prescription the pharmacist usually fills it with the lowest cost generic drug and does not look at the label. And even if a disease is listed on one particular brand of generic drug, the pharmacist does not know the patients' diagnosis and, therefore, cannot abide by the labeling.

On the other hand, when companies are willing to support the research necessary to add a rare disease to the label of a patented drug, they often find the "Supplemental NDA" process too burdensome. In too many cases, the FDA appears to consider these applications as a low priority and seems to take an inordinate amount of time to approve them. **While there is substantial public and political pressure put on the agency to approve new drugs, there is very little in the way of timely action on Supplemental NDA's.**

There seems to be no sense of urgency to do anything about this problem. Unfortunately, for the American patients and families who find themselves deeply in debt because their insurance will not reimburse them for an "unapproved" treatment, the day arrives when they can no longer afford the medical care they need -- a sad predicament for anyone with a serious or chronic disease.

It seems that no one at the FDA currently has responsibility for monitoring this problem, although, they do have the responsibility to police the market for "off-label" promotional activities such as advertising. The agency should be in the practice of soliciting

Supplemental NDAs from companies when they know that "off-label" use is widespread. The drug divisions at the FDA should work in tandem with the advertising division to monitor the problem and find solutions. The acne medication, *Retin-A*, is an example of how this could work. This year, the FDA approved the drug for the prevention of wrinkles, but only after the agency prosecuted the manufacturer for unlawful promotional activities. When the agency knows that dermatologists are regularly prescribing the drug for an "off-label" use, a special division in charge of Supplemental NDAs should work with the company to assure that they apply for the new indication -- especially, when a marketing violation is well known.

***Ineffective* "Off-Label" Use**

Another quite devastating case involved companies that were subtly promoting the "off-label" use of calcium channel blockers (approved to treat high blood pressure) for the prevention of heart attacks after a patient's first heart attack had occurred. This "off-label" use became so pervasive, millions of heart attack victims were prescribed these drugs until the NIH finally supported a controlled clinical trial proving to everyone's amazement that the patients fared better on other approved drugs than those on the calcium channel blockers. It has been suggested that this study alone proves the importance of FDA's regulatory authority over "off-label" promotion, and the importance of supplemental reviews and approvals. Thousands of people may have suffered unnecessary second heart attacks because appropriate studies were not conducted with these drugs. If doctors had only known that calcium channel blockers were ineffective in preventing second heart attacks, they could have prescribed alternative, effective medicines. Unfortunately, it was the American taxpayer who finally had to underwrite the research that should have been done by the manufacturers.

***Unsafe* "Off-Label" Use**

Even worse, tens of thousands of heart patients were killed by a family of drugs approved to treat irregular heartbeats, known as antiarrhythmic drugs. Approved for the most severely ill patients, these drugs were often prescribed "off-label" for patients with only minor irregular heartbeats. Typically, the irregular heartbeats were so minor the patient

couldn't even detect them. It took special 24-hour heart monitoring to identify the irregular beats. Researchers believed these very mild irregular heartbeats could without warning blossom into lethal irregular beats and death. It thus seemed perfectly reasonable to treat these mild cases. Papers supporting this theory were repeatedly published in all the best medical journals, but nobody had done the proper clinical testing. Unfortunately, the theory was wrong. Again, the NIH finally performed a clinical trial which proved conclusively that these drugs caused cardiac arrest instead of preventing it.

Pediatric "Off-Label" Drug Use

Regarding pediatric uses, most drugs sold in the U.S. are not approved for use by children because they have not been tested in pediatric populations. Except for a few common childhood diseases such as asthma, attention deficit disorder, infections, etc., serious and chronic diseases in children are quite rare. Pharmaceutical companies would not ordinarily spend the money, for example, to study a hypertension drug used in a childhood disease when everyone thinks that hypertension is an adult disease. However, there are many pediatric rare diseases that are treated with hypertension drugs not only for high blood pressure but for heart abnormalities, neurological disorders, etc. It is important that pediatric uses be studied for these drugs so that appropriate dosages and possible side effects are known to physicians.

Insurance Reimbursement

The reimbursement problem associated with "off-label" uses of certain drugs for the ***elderly*** has been somewhat solved in the Medicare population by the ***"Three Compendia Rule."*** That is, Medicare will reimburse for a drug that is being used for an "off-label" indication, if that use is recognized as effective in one of three medical compendia: the *AMA Drug Evaluations,* the *American Hospital Formulary Service's Drug Information,* and the *United States Pharmacopeia Dispensing Information (USPDI).* Unfortunately, problems remain because a) the AMA's *Drug Evaluations* is no longer published, and b) the private health insurance market is not compelled to follow this Medicare rule. Some insurers will reimburse for some compendia uses, but they ignore others.

Mr. Chairman, patients are getting the short end of the stick. We are creating a two-tiered system when some patients who are rich enough to pay for their prescriptions themselves, or are lucky enough to have a compassionate insurance company, can obtain treatment while those who are unlucky or poor cannot. Understanding that this Subcommittee does not have jurisdiction over the insurance industry, we simply want to point out that in the absence of a ground swell of supplemental new drug applications, further reform of the health insurance industry is absolutely necessary.

Solutions to the Problem

The ultimate solution -- what American patients and their doctors *really* need -- is to put "off-label" diseases on the labels of marketed drugs. Of course, this would require that appropriate research has to be conducted to prove the drug is safe and effective and proper doses for the secondary condition are clearly delineated on the label. But this will not happen without **1) raising the priority of Supplemental NDA reviews inside of the FDA**, and **2) financial incentives to the pharmaceutical industry**. NORD suggests the following solutions:

Role for the Food and Drug Administration:

- Remove the "gag rule" that prevents the FDA from talking honestly with the public about the mere status of supplemental applications. Right now, if a consumer or physician inquires about why their disease is not included on a drug's label, the FDA is not allowed to say whether or not the manufacturer has applied for a Supplemental NDA, nor give the status of the review process. Even if the FDA has disapproved an application because they know a drug is not safe or not effective, they are not allowed to tell the American public the truth. The silence of the FDA endangers the public health. Congress should remove unreasonable restrictions on information.

- Require the FDA to monitor and identify "candidate" drugs with substantial "off-label" uses. A special unit for "off-label" surveillance should be created to coordinate with the Advertising and Labeling Division to "red flag" these products.

- One way to prioritize the review of supplemental indications, which consist primarily of clinical data, would be to assign a small number of FDA reviewers to a separate division or unit where review of Supplemental NDAs would be the priority. There is no reason that supplemental applications should be put aside to await review by division personnel who reviewed the original NDA. Once a drug is marketed, a great deal is already known about its safety. Thus, a self-contained **Supplemental Review Division** could review these applications more speedily if they do not have to worry primarily about meeting deadlines for review of more complicated New Chemical Entities (NCEs).

- Administratively, the FDA should require centers and divisions to operate under the same rules for review of Supplemental NDAs. Currently, we sense that some areas within the FDA give a lower priority to Supplemental NDAs and they are biased against them. Division directors should not be allowed to make judgements based on their personal opinion of the importance or significance of a particular drug. Supplemental applications should be categorized as "standard" or "priority" reviews. SNDAs for "serious and life-threatening illnesses" should receive priority status, regardless of the condition's prevalence.

- Improve the supplemental review process. In general, companies should have an easier, quicker application process for Supplemental NDAs than they do now. However, modifications to the review process should not include an abandonment of the efficacy standard nor bypass thorough, independent review of data and information relevant to the new use. More rapid reviews will help reduce disincentives for industry to submit applications seeking approval for "off-label" uses, but only if unsolicited dissemination of information by the manufacturer continues to be limited to FDA approved indications.

Role for Congress:

- Congress should create incentives to entice manufacturers into adding new indications to the labeling of marketed drugs for the treatment of serious and life-threatening conditions, particularly rare diseases and pediatric uses. These incentives should include a generous tax credit for the cost of well-controlled clinical trials that are required by the FDA. If Congress removes the economic disincentives that make companies hesitant to invest in supplemental research, there would be no excuse for companies not to file a Supplemental NDA.

  However, Congress should not create financial incentives that are disproportionate to the amount of money a company must invest for a supplemental approval. The amount of a tax credit should also have a direct relationship to the needs of society. For example, getting a marketed drug approved as a diet, wrinkle or baldness remedy is not as important as a supplemental approval for life-threatening diseases such as Lou Gehrig's Disease, cystic fibrosis, cancer, or AIDS.

Role for Industry:

- The pharmaceutical industry must become more responsive to the needs of medically disenfranchised Americans. For millions of men, women, and children suffering with serious, chronic and life-threatening health problems, drug companies often hold the key to their future. When a drug is known to have an important "off-label" use, manufacturers should have a social responsibility for the safety and effectiveness of their products. Only the industry has enough resources to fund the necessary research to assure physicians and patients that the treatment is safe and effective at appropriate doses in a target population. Indeed, it is true that all companies must keep a close eye always focused on the "bottom line," but they also have a responsibilty to assure American patients that they will do no harm. Ignoring "off-label" uses, which the industry knows is pervasive, certainly causes harm.

In conclusion, Mr. Chairman, I would like to commend the Subcommittee for caring about the estimated 20 million Americans with rare "orphan diseases." In 1983, with passage of the Orphan Drug Act, our nation only began to solve the problems associated with rare, but serious health conditions. Today, there remains much more work to be done. The 1989 report of the ***National Commission on Orphan Diseases*** recommended that Congress create a central **"Office for Rare Diseases"** that would coordinate the activities of private industry with many federal rare disease programs which operate independently now. This office would have saved time and resources by avoiding duplication and waste. For example, if the offfice had been created as the Commission suggested, they could have coordinated the FDA's "off-label" concerns with activities at the NIH, and urged drug manufacturers to submit SNDAs on many marketed drugs. Today, however, the federal government does not even obey its own mandates in the Orphan Drug Act for regular meetings of the **Orphan Products Board (OPB)** nor its annual report to Congress.

Clearly, in addition to the "off-label" use of drugs, other important issues persist. Congress must turn a new corner and renew its commitment to people with orphan diseases through a comprehensive, strategic action plan for rare disorders. Thank you for your dedication to helping people with orphan diseases.

Attachment "A"

A SAMPLE OF "OFF-LABEL" USES OF DRUGS FOR TREATMENT OF RARE DISEASES

Disease Name: Aicardi Syndrome

Aicardi Syndrome is an extremely rare congenital disorder in which the structure linking the two cerebral hemispheres of the brain (corpus callosum) fails to develop. Absence of the corpus callosum is associated with frequent convulsive seizures, abnormalities of the retina and the thin membrane (choroid) that covers the retina of the eyes, and/or mental retardation.

Drug Therapy: adrenocorticotropic hormone (ACTH)
On-label Indications: West syndrome and certain seizure disorders, multiple sclerosis, endocrine disorders, acute episodes of rheumatic disorders, collagen diseases, inflammatory dermatologic and eye diseases, certain respiratory and hematologic disorders, leukemia and lymphomas, ulcerative colitis.

Drug Therapy: valproic acid (Depakene, Depakote)
On-label Indications: Indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures and adjunctively in patients with multiple seizure types that include absence seizures (Note: Many anticonvulsant medications are approved for one or two types of seizures, but are used for other types of seizures that are not on the label).

Disease Name: Fibrosing Alveolitis

Fibrosing Alveolitis is a rare inflammatory disease of the lungs characterized by the abnormal formation of fibrous tissue between tiny air sacs (alveoli) or ducts in the lungs. Symptoms may include coughing, rapid, shallow breathing occurring with moderate exercise, and an abnormal bluish skin coloration.

Drug Therapy: azathioprine (Imuran)
On-label Indications: Indicated as adjunct for the prevention of rejection in renal transplantation. Indicated for the management of severe, active rheumatoid arthritis unresponsive to rest, aspirin or other nonsteroidal anti-inflammatory drugs.

Disease Name: Alternating Hemiplegia of Childhood

Alternating Hemiplegia of Childhood (AHC) is a rare neurological disorder characterized by frequent, temporary episodes of paralysis on one side of the body (hemiplegia), temporary paralysis of the muscles that control eye movements (transient ocular palsies), sudden, involuntary movements of limbs and facial muscles (choreoathetosis) and/or excessive sweating with changes in skin color and body temperature (autonomic nervous system dysfunction).

Drug Therapy: calcium channel blockers (e.g., Cardizem, Norvasc, Procardia)
On-label Indications: Treatment of hypertension and angina.

Disease Name: Acquired Agranulocytosis

Acquired Agranulocytosis is a rare drug-induced blood disorder characterized by a severe reduction in the number of white blood cells (granulocytes) in the circulating blood. Symptoms may include increased susceptibility to a variety of bacterial infections (causing flu-like symptoms) and painful ulcers in mucous membranes that line the mouth and/or the gastrointestinal tract.

Drug Therapy: gammaglobulin (Immune Globulin [Human])
On-label Indications: Indicated for the treatment of Hepatitis A, measles, immunoglobulin deficiencies, varicella and rubella.

Disease Name: Ahumada-Del Castillo Syndrome

Ahumada-Del Castillo Syndrome is a rare endocrine disorder that affects females and is characterized by impaired function of the pituitary and hypothalamus glands. Symptoms may include abnormal production of breast milk (galactorrhea) without childbirth and nursing, lack of normal ovulation (anovulation) and the lack of regular menstrual periods (amenorrhea).

Drug Therapy: pergolide mesilate (Permax)

On-label Indications: Indicated as adjunctive treatment to levodopa/carbidopa in the management of Parkinson's disease.

Disease Name: Amyloidosis

Amyloidosis is a group of metabolic disorders characterized by the abnormal accumulation of a certain fibrous protein (amyloid) in many tissues of the body. Amyloid accumulations, which may be localized, general, or systemic, may cause the affected organ(s) (e.g., intestinal tract, heart, liver, spleen, kidneys, etc.) to malfunction.

Drug Therapy: colchicine

On-label Indications: Indicated for the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout.

Disease Name: Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a neuromuscular disease of the nerves that control the function and movements of skeletal muscles (motor neurons). Symptoms, which typically affect both upper and lower motor neurons, include muscle weakness, clumsy movements, difficulty swallowing (dysphagia) and speaking (dysarthria), and progressive wasting of muscles that have lost their nerve supply.

Drug Therapy: diazepam (Valium)

On-label Indications: Indicated for the management of anxiety disorders or the short-term relief of symptoms of anxiety. In acute alcohol withdrawal, may be useful in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. Relief of skeletal muscle spasm due to local pathology; atheosis and stiff man syndrome. May be used adjunctively in convulsive disorders although it has not proved useful as the sole therapy.

Drug Therapy: pyridostigmine bromide (Mestinon)

On-label Indications: Treatment of Myasthenia Gravis.

Drug Therapy: gabapentin (Neurontin)

On-label Indications: Indicated as adjunctive therapy for the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

Disease Name: Aplastic Anemia

Aplastic Anemia is a rare blood disorder characterized by decreased function of the bone marrow that results in abnormally low levels of all the cellular elements of the blood (pancytopenia). In some cases, the disorder may affect primarily single cell lines (i.e., red blood cells, white cells, or platelets). The initial symptoms may include increasing weakness, fatigue, recurrent or persistent infections, and/or lethargy.

Drug Therapy: cyclosporin (Neoral, Sandimmune)

On-label Indications: Indicated for the prophylaxis of organ rejection in kidney, liver and heart allogenic transplants.

Drug Therapy: cyclophosphamide (Cytoxan)

On-label Indications: Treatment of certain cancers including malignant lymphomas; multiple myeloma; leukemias; mycosis fungoides (advanced disease); neuroblastoma (disseminated disease); adenocarcinoma of the ovary; retinoblastoma; and carcinoma of the breast. Also indicated for the treatment of biopsy-proven "Minimal Change" nephrotic syndrome in children.

Disease Name: Tourette Syndrome

Tourette Syndrome is a hereditary neurological movement disorder characterized by involuntary rapidly repeated movements (tics and twitches) and uncontrollable vocalizations.
Drug Therapy: clonidine (Catapres)
On-label Indications: Indicated for the treatment of hypertension.

Drug Therapy: guanfacine hydrochloride (Tenex)
On-label Indications: Indicated for the treatment of hypertension.

Drug Therapy: fluphenazine hydrochloride (Prolixin)
On-label Indications: Indicated for the management of psychotic disorders.

Drug Therapy: imipramine hydrochloride (Tofranil)
On-label Indications: Indicated for relief of depression and childhood enuresis (bed wetting).

Drug Therapy: desipramine hydrochloride (Norpramin)
On-label Indications: Indicated for the treatment of depression.

Drug Therapy: nortriptyline hydrochloride (Pamelor)
On-label Indications: Indicated for the treatment of depression.

Drug Therapy: fluoxetine hydrochloride (Prozac)
On-label Indications: Indicated for the treatment of depression and obsessive-compulsive disorder (OCD).

Drug Therapy: clomipramine hydrochloride (Anafranil)
On-label Indications: Indicated for the treatment of obsessive-compulsive disorder (OCD).

Drug Therapy: sertraline hydrochloride (Zoloft)
On-label Indications: Indicated for the treatment of depression.

Disease Name: Tinnitus

Tinnitus is a condition characterized by the sensation of sound for which there is no external source. Individuals with Tinnitus perceive sound when no environmental or external sounds are present. These sounds have been described as clicking, buzzing, and/or ringing.
Drug Therapy: oxazepam (Serax)
On-label Indications: Indicated for the management of anxiety disorders. Alcoholics with acute tremulousness, inebriation, or with anxiety associated with alcohol withdrawal.

Drug Therapy: clonazepam (Klonopin)
On-label Indications: Treatment of Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures, absence seizures (petit mal) who have failed to respond to succinimides.

Drug Therapy: sodium amylobarbitone
On-label Indications: Hypnotic drug.

Drug Therapy: flunarizine hydrochloride
On-label Indications: A calcium channel blocker used to treat hypertension and angina.

Drug Therapy: eperisone hydrochloride
On-label Indications: Centrally-acting muscle relaxer.

Disease Name: Essential Thrombocytopenia

Essential Thrombocytopenia is a rare blood disease characterized by abnormally low levels of circulating blood platelets and a shorter than normal platelet survival time (i.e., 10 days). Symptoms may include a tendency to bleed excessively into the skin or mucous membranes, especially during menstruation.
Drug Therapy: immune globulin
On-label Indications: Indicated for the maintenance treatment of patients with immunodeficiencies. Treatment of acute and chronic idiopathic thrombocytopenic purpura (ITP).

Disease Name: Essential Thrombocythemia

Essential Thrombocythemia is a rare disorder of blood platelet production characterized by abnormally elevated levels of circulating blood platelets. Major symptoms may include active bleeding, the formation of blood clots (thrombosis) and/or abnormal enlargement of the spleen (splenomegaly).
Drug Therapy: hydroxyurea (Hydrea)
On-label Indications: Significant tumor response to Hydrea has been demonstrated in melanoma, resistant chronic myelocytic leukemia and recurrent, metastatic, or inoperable carcinoma of the ovary. Hydrea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

Drug Therapy: melphalan (Alkeran)
On-label Indications: Indicated for the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary.

Drug Therapy: busulfan (Myleran)
On-label Indications: Indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia.

Disease Name: Thomsen Disease

Thomsen Disease is a rare inherited neuromuscular disorder characterized by difficulty in initiating voluntary movements, followed by prolonged muscle contraction. Symptoms may include muscle stiffness (affecting the entire body), muscular rigidity, uncontrolled involuntary muscle movements (spasms) and slowness in chewing, swallowing, talking, and walking.
Drug Therapy: tocainide hydrochloride (Tonocard)
On-label Indications: Treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment of the physician, are life-threatening.

Disease Name: Tardive Dyskinesia

Tardive Dyskinesia (TD) is a neurological movement disorder resulting from use of neuroleptic drugs used to control psychiatric or gastrointestinal disorders. Tardive Dyskinesia is characterized by involuntary and

abnormal movements of the jaw, lips and tongue including grimacing, sticking out the tongue, sucking or "fish-like" movements of the mouth.
Drug Therapy: lithium carbonate (e.g.Lithonate)
On-label Indications: Treatment of manic-depressive illness.

Drug Therapy: bromocriptine mesylate (Parlodel)
On-label Indications: Treatment of hyperprolactinemia-associated dysfunctions including amenorrhea with or without galactorrhea, infertility or hypogonadism. Treatment of patients with prolactin-secreting adenomas, acromegaly and Parkinson's disease.

Drug Therapy: baclofen (Lioresal)
On-label Indications: Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus and muscular rigidity.

Drug Therapy: methyldopa (e.g., Aldomet)
On-label Indications: Treatment of hypertension.

Drug Therapy: valproic acid (Depakene, Depakote)
On-label Indications: Treatment of simple and complex absence seizures and adjunctively in patients with multiple seizure types that include absence seizures.

Drug Therapy: clonidine (Catapres)
On-label Indications: Indicated for the treatment of hypertension.

Drug Therapy: propranolol hydrochloride (Inderal)
On-label Indications: Indicated in the management of hypertension, the long-term management of angina pectoris due to coronary atherosclerosis, cardiac arrhythmias, reduction of cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable. Also indicated for the prophylaxis of common migraine headache, the management of familial or hereditary essential tremor, and management of hypertrophic subaortic stenosis, especially the treatment of exertional or other stress-induced angina, palpitations, and syncope. In patients with Pheochromocytoma, may be useful as adjunctive therapy if the control of tachycardia becomes necessary before or during surgery.

Drug Therapy: amantadine hydrochloride (e.g., Symmetrel)
On-label Indications: Prophylaxis and treatment of infection caused by various strains of influenza A. Treatment of parkinsonism (idiopathic Parkinson's disease [paralysis agitans], postencephalitic parkinsonism, and symptomatic parkinsonism) and drug-induced and extrapyramidal reactions.

Drug Therapy: clonazepam (Klonopin)
On-label Indications: Treatment of Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures, and absence seizures (petit mal).

Drug Therapy: nifedipine (e.g., Adalat)
On-label Indications: Management of vasospastic angina and chronic stable angina (classical effort-associated angina).

Mr. TOWNS. Thank you very much, Ms. Meyers. Dr. Kennedy.

Mr. KENNEDY. Thank you, Mr. Towns. I am William J. Kennedy, vice president of drug regulatory affairs at Zeneca Pharmaceuticals in Wilmington, DE. Zeneca is a research-based company that has a distinguished record in providing innovative quality health care products for patients and physicians.

Today, I appear before you on behalf of the Pharmaceutical Research and Manufacturers of America, PhRMA, the trade association for the research-based pharmaceutical industry. PhRMA companies are world leaders in drug development, in discovery, responsible for approximately 90 percent of the drugs that are discovered.

I greatly appreciate the chance to testify on supplemental new drug applications, specifically applications for new indications of already approved drugs. I have submitted a complete written testimony for the record and I will be very brief and will limit my comments here to four major points.

There is a growing recognition that the supplemental NDA process needs to be fixed. Industry has recognized this and has recommended changes for several years. Congress has identified this as a problem. This hearing is proof of that.

In addition, legislation is pending in both the House and the Senate that acknowledges the need for changes in the review and the approval of supplemental NDAs. Patient and medical groups, as evidenced by their presence here today, want reform. And the FDA has recognized this, as noted in the September 5th remarks by Deputy Commissioner for Policy Bill Schultz to the Food and Drug Law Institute.

We thank the FDA for recognizing that the supplemental NDA process needs fixing and look forward to working with them to do so. The problem, while serious, is not rampant within the FDA. Some divisions have excellent records on reviewing and approving supplemental NDAs, but other divisions have review times that are considered unacceptable by all of the interested parties.

So the FDA has the solution to the review of supplemental NDAs within its organization within the divisions that are working well. FDA can and should be able to identify and formalize the best practices in those divisions that are excelling.

FDA must then require these best practices be the standard in all of the divisions and move the approval of supplemental NDAs in all drug classes in a timely fashion. This goal must be articulated and formalized in regulation, guidance and/or legislation.

But even when the supplemental NDA review process works efficiently for all drugs, the need for dissemination of information on off-label uses will continue because, as has been pointed out several times this morning, state-of-the-art medicine will always be ahead of the information that is in a drug's package insert.

Dissemination of information is education. It is not promotion. And the pharmaceutical industry plays a valid and a vital role in providing that education.

I thank you for allowing me to testify and will answer any questions you might have.

[The prepared statement of Mr. Kennedy follows:]

Statement PhRMA

TESTIMONY OF WILLIAM J. KENNEDY, PH.D.

BEFORE THE HUMAN RESOURCES AND INTERGOVERNMENTAL AFFAIRS SUBCOMMITTEE

GOVERNMENT REFORM AND OVERSIGHT COMMITTEE

SEPTEMBER 12, 1996

Good morning, Chairman Shays and members of the Subcommittee. I am Dr. William J. Kennedy, Vice President for Drug Regulatory Affairs at Zeneca Pharmaceuticals, Wilmington, Delaware. Zeneca Inc. is $2.8 billion bioscience business with approximately 6,000 employees at 53 locations in 24 states. Zeneca Inc. is a wholly-owned subsidiary of the UK-based Zeneca Group PLC, a major $7.6 billion international bioscience business engaged in the research, development, manufacture and marketing of ethical (prescription) pharmaceutical, agriculture, and specialty products and the supply of healthcare services.

Zeneca has a distinguished record in providing innovative quality health care products for physicians and patients. This began when Sir James Black, working in our laboratories, gave the world receptor-based research. For this, he won the Nobel prize in medicine. Our laboratories have also produced Diprivan, an injectable anesthetic with rapid onset and rapid recovery. We are probably most proud of our contribution to the treatment of cancer. Nolvadex, the most widely used drug in the treatment of breast

cancer, has changed the lives of countless women and their families. We also developed Zoladex for the treatment of prostate cancer.

I feel well-placed to discuss regulatory reform at FDA as an employee of one of the most successful pharmaceutical companies in the last 12 months. Against a background in which the FDA approved an average of 25 New Chemical Entities (NCEs) per year, Zeneca has received more than 10% of these approvals. These have been significant drugs: Casodex, the first oral treatment for prostate cancer, approved in 10 months; Arimidex, a member of a new class of breast cancer drugs, approved in 13 months; Merrem, one of only three new anti-biotics approved in the last three years. We have also been involved with our licensing partners in achieving approval of Sular, a cardiovascular drug, and Kadian, a long-acting morphine product, specific for the management of cancer pain.

Germane to today's hearing, we have also been successful in obtaining supplemental NDA approvals, including one for a long-acting formulation of Zoladex, our prostate cancer treatment drug.

I am here today representing the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade association for the research-based pharmaceutical industry. PhRMA companies are world leaders in drug development and discovery, responsible for more than 90% of drugs discovered. I greatly appreciate the chance to appear before you and testify on the issue of Supplemental New Drug Applications (SNDAs). There are two types of SNDAs -- those for new indications and those for manufacturing changes. I will focus today on new indications.

The drug discovery, development, and approval process is time-consuming and expensive. It has taken as long as 15 years and $500 million to secure approval for a new drug in the U.S. FDA initiatives, including the Prescription Drug User Fee Act (PDUFA) and others similar to those proposed in several pieces of legislation are shortening the time frame but there is still room for improvement in these areas. The drug business is a high-risk endeavor, but it is also a high-reward endeavor. In recent months, pharmaceutical companies have introduced the new protease inhibitors that are showing great success against the virus that causes AIDS, as well as new drugs for cancer, Lou Gehrig's disease and multiple sclerosis.

Because what we do is so expensive, time-consuming, and important to patients, we in the industry believe that the process of making new drugs available must be as efficient as possible, and we are hopeful that legislation will be passed this Congress to assist the FDA as it prepares for the 21st century.

New Indications

Equally important, as evidenced by this Subcommittee hearing today, is the continued development of these new drugs, and the approval of Supplemental New Drug Applications (SNDAs) for new indications. There appear to be numerous obstacles to the rapid approval of SNDAs. A report from the Labor and Human Resources Committee mark-up of June 20, 1996 noted that "it takes as long or longer for the FDA to review supplemental applications as it does to review applications for initial product approvals. These lengthy review times serve as a disincentive to drug [...] manufacturers to file supplemental applications." Because of user fees and FDA's efforts to meet its user fee

goals, SNDAs are being reviewed more rapidly, but in general, review of supplemental applications has not been a priority at FDA.

There are examples where FDA has approved SNDAs with admirable efficiency, the best that can be expected. In others, the time to approval is close to acceptable but could be improved. Finally, as you've already heard from experts at Tufts University and the GAO, there are approval times that are just unacceptable to the industry, to patients, to you in Congress, and to FDA. What we should all work toward is helping the agency identify the best practices that are providing the most efficient approvals so that the standard time to approval in the future is as close as possible to the best times achieved now.

Why is there this disparity in approval times? Because there are inconsistencies from FDA division to FDA division in the requirements for an SNDA. There are even inconsistencies within divisions regarding requirements. What is happening, what are the consequences, and what can be done?

The worst case can be due to the strict requirement that efficacy be proven for each new indication in the same way as it is in the original NDA -- by two large, well-controlled, double-blind clinical trials. The science of clinical research and study design has changed greatly in recent years. One large, well-controlled clinical trial, supported by information learned in other smaller supportive trials, can in most cases provide ample evidence to prove efficacy. FDA reform legislation now before the Congress should reflect this current scientific reality. But whatever the efficacy standard is for an NDA, requiring the same

stringent standard in an efficacy supplement is not efficient or practical, and it slows down the SNDA process, especially when safety has already been established.

This is totally unacceptable in the treatment of cancer. Upon approval by FDA, a cancer drug is seldom labeled for use in all cancers. It is usually labeled for use in one type or sub-type of cancer, but oncologists often prescribe the drug for cancer patients not in the approved type. In fact, such cutting-edge organizations as the National Cancer Institute (NCI) and the National Institutes of Health (NIH) routinely include drugs with unapproved indications in their recommended standard protocols for the treatment of cancers.

Once a drug is on an NCI or NIH protocol, many, but not all, oncologists begin using the drug, and a wealth of information becomes available. This expertise should be considered in the approval for new indications. This has been the norm rather than the exception in the approval of additional indications for cancer drugs, but has not been the case for other drug classes. We owe just as much attention to drugs in other classes, which may help patients suffering from other devastating diseases.

Solution to the Problem

The solution -- in all drug classes, not just in those for politically correct diseases -- is simple. When a drug becomes the standard of treatment, it should be included in the package insert so that correct and appropriate information can be provided to all practitioners to safely and effectively treat patients.

FDA has recently recognized that the current SNDA process also hampers effective treatment for children and has moved to remove these obstacles. For a number of reasons, including more stringent regulatory requirements, ethical questions and lack of incentives,

drugs intended for adults are seldom tested on children, even though those drugs may commonly be used in children. In much the same way that limitations once existed for the evaluation of drugs in women, FDA is evaluating the requirements and considering incentives to sponsors that will encourage the earlier evaluation of a new drug in children. The industry applauds this action by FDA and encourages the rapid conclusion of this exercise. Until that is accomplished, trials in children will remain technically more difficult, and the child will have to endure the blood sampling, urine collections and other unpleasant procedures that are part of the current process.

There is anecdotal information that health care providers and hospitals recognize the inadequacy of the current system. It used to be that health care providers would deny payment for uses that were not approved. The reason -- economics. They are now beginning to rethink their policies for the same reason. They used to feel that money could be saved by limiting use of newer, generally more expensive drugs. Now they are starting to recognize that the cost effective treatment of a disease should include the best treatment. How are leaders in health care and hospitals doing this? They are reviewing the literature, attending scientific and medical meetings, and making their own decisions through their formulary committees. In addition to the older drugs that have wider ranges of indications, they are adding to their formularies newer drugs that have limited indications, allowing physicians to make the correct choice. Shouldn't all patients, not just those covered by enlightened health care providers, have the same standard of care provided to them? They can if SNDAs are offered a higher, more consistent priority and review.

Current Legislative Proposals

Both House and Senate FDA reform bills would address the need to reform the SNDA process. H.R. 3199, the House bill, would require the Secretary of Health and Human Services to consider clinical practice, as reported in studies in scientific journals or in information included in compendia. The Senate bill, S. 1477, would require the FDA to establish performance standards for review of supplemental applications and clarify the data requirements for an SNDA. The Senate bill would designate a person within each FDA center, like the Center for Drug Evaluation and Research, who would be responsible for ensuring timely action on supplemental applications. The Senate bill also mandates creation of programs to foster collaboration between FDA, NIH and medical groups. The purpose of this collaboration would be to identify studies that could be used to support an SNDA and encourage the submission of SNDAs based on this information. All of these provisions would go far to improving the SNDA process and I hope that they pass as part of FDA reform legislation. The Senate bill would also offer incentives for conducting the clinical trials necessary to support pediatric indications in a drug's label, and this provision should be supported.

Dissemination of Information

Until approval of an SNDA, use of the product for a non-approved indication is considered "off-label." Off-label use is not prohibited -- doctors may prescribe an FDA-approved drug for any condition. As a result, supplemental approvals for new indications are inextricably linked to off-label use and dissemination of information about off-label use,

and I will conclude my statement with a few remarks about off-label use and information dissemination.

It must be recognized that off-label use is common in medicine -- as the new GAO report states, 80-100% of cancer, pediatric and rare disease treatment is off-label, and off-label use is the norm in treating many other diseases.

Dissemination of information about off-label use to medical professionals is <u>not</u> promotion of off-label use -- it is education by facilitating the availability of third-party information that has already been published, particularly in peer-reviewed journals. There are more than 3,000 medical journals published, and no practicing physician has time to read every one. The FDA currently prohibits dissemination of information on unapproved uses by no one other than pharmaceutical manufacturers, meaning that a drug company that may be uniquely informed about a particular drug may not send out reprints of journal articles to doctors unless the doctor specifically calls and requests the article.

PhRMA believes, as do I, that education of physicians does not stop when they leave medical school and dissemination of information on all meaningful uses is necessary to make the most up-to-date medical information available to doctors, so that patients can receive the most effective treatment. Please remember that a physician cannot request information that he does not know exists.

In the debate over dissemination of information, some have suggested that manufacturers would limit disseminated information to positive studies on their drugs. This is not consistent with the principles expressed and supported by PhRMA members. We have always supported and encouraged dissemination of balanced information --

positive, negative, and neutral, with the goal being that fully educated physicians will make the right choices for their patients.

Thank you for allowing me to testify and I would be happy to answer any questions.

Mr. TOWNS. Thank you very much, Dr. Kennedy. Dr. Runowicz, I know you have to leave, so let me just ask you a couple questions and then you may depart.

You indicate that because of the FDA approval rate cannot keep pace with the practice of cancer medicine, a number of accommodations should be made in FDA regulatory procedures. Is your primary recommendation that the FDA restrictions on off-label promotions, including information-sharing, should be lifted?

Dr. RUNOWICZ. Well, I think that the word promotion is pejorative and misleading. I think that dissemination can be education. When there is a new drug that has been shown to be effective in other cancers and then clinical trials show it to be effective in, say, another cancer like ovary cancer, it is very important that that information be disseminated to the medical community so that patients can benefit from that new information.

I think just as an aside that what I have heard this morning, and I think is very misleading, is that these secondary applications are as if they are pulled out of thin air when, in fact, if you look at the research that is done on these secondary applications, this is very stringent research. And doctors look at this research very critically and that is how a secondary indication develops. It is not that we just sit down and say, well, I would like to try this drug on this patient because it has just been released. It is based on good, scientific data. And that data needs to get out quickly to the community through dissemination and education.

Mr. TOWNS. Should we be concerned about any negative impact on patients' health because of off-label drug use?

Dr. RUNOWICZ. I would turn that around the other way and I would say that the standard of practice in cancer is that these secondary uses benefit the patients. Not to focus entirely on cancer, but if you look at the issue of hormone replacement, for example, estrogen is not approved for the prevention of heart disease; yet we know from good prospective trials that there is very strong evidence of heart prevention, heart disease prevention.

And yet that is an off-label indication that I would say most physicians, primary care providers, are now using to persuade women. And I can assure you that they are not signing informed consent because this is based on very good clinical evidence.

Mr. TOWNS. Let me just ask you one other thing and then I will be delighted to say to you thank you very much for your participation. Of course, it was suggested here, I think, by Dr. Kauffman that the Congress should come up with a panel that would sort of approve, look at, and help to expedite.

What is your reaction to that?

Dr. RUNOWICZ. Well, I think that legislative action may not be necessary. I think that already the FDA has a lot of these programs available to them to expedite review and that they can do this internally without further regulations.

Mr. TOWNS. Well, let me thank you very much for your testimony, and I know you have to leave. So thank you very, very much. We appreciate your participation.

Let me just move to you, Dr. Kauffman, on that note. You indicated that, first of all, if the Congress decided to do that, I mean, how would these people be appointed?

Dr. KAUFFMAN. I don't have a specific recommendation for that, but I think they could be nominated by their respective professional groups from which they derived. They could be nominated from a number of sources.

But I think in response to the comments here, I think it is a little different for children than it is for some of the other orphan groups that we are talking about this morning. Children are the only one of the three groups we are talking about here this morning that do not have drugs labeled for them solely on the basis of their age. The others are based on the disease they have, but this is based solely on the age. And approximately 25 percent of the population in this country fall into the age group that we call children.

So I think that representation for children's issues in FDA decisions and considerations is very important. Currently, to my knowledge, among the FDA advisory groups there is not one that is focused on pediatric issues. There may be a pediatrician on one of the other advisory groups, but in terms of an advisory group to focus solely on pediatric issues, to my knowledge, there is not such a group.

Mr. TOWNS. Did you want to add anything to that?

Ms. MEYERS. Well, I think if anybody just walks into any drug store in the country and just goes down the aisle that sells cold medicines and cough syrups, if you read the labels on them, you will find out they are not approved for children. It cautions parents not to give them to children under 8 or under 12. And you could probably take every single product off the shelf and find that same warning on each label.

Mr. TOWNS. After this question I am going to yield back to you, Mr. Chairman. Let me just ask Dr. Kennedy one thing.

You said something that really struck me. You said that SNDA and the NDA needs to be fixed. Now, do you have any specific ideas as to how that could be fixed?

Mr. KENNEDY. Well, yes, I do and they have been conveyed in a number of different forms. As I noted in my testimony, the FDA has some divisions which are working at an exceptional rate. They are providing input to the sponsors before investigations start, before we start looking for supplemental indications. They work with the sponsor while the development program is underway and they work with the sponsor to expedite the review and the approval of the supplemental NDA when it comes into the FDA.

The unfortunate thing, Mr. Towns, is that a lot of the information that has been conveyed this morning is based upon information at a cutoff of 1994. The regulatory reform that is being proposed in Congress and the initiatives that have been taking place under PDUFA have changed that picture considerably. And I think it should be taken into consideration. The standard of best practice does exist at the FDA. Identify it, formalize it, expand it, enforce it.

Mr. TOWNS. Thank you very much. Mr. Chairman, I yield back.

Mr. SHAYS. What I would love to ask the three of you, and I am sorry I didn't hear your testimony, but I would like to know whether you think the status quo is better than a feared solution and/or whether you think there are some definite solutions that we

should take, and then I would like each of you to outline as succinctly as possible. I mean, we have already set the stage for the last two panels, so I will just start with each of you.

First, Dr. Kauffman, do you fear the solution more than the status quo?

Dr. KAUFFMAN. No.

Mr. SHAYS. Ms. Meyers.

Ms. MEYERS. We need a solution.

Mr. KENNEDY. No, we don't fear it.

Mr. SHAYS. Pardon me. You don't fear it?

Mr. KENNEDY. No, we don't fear a solution.

Mr. SHAYS. OK. So each of you, you have made it in your statements, but state as succinctly as possible what you think the particular solution is or a step that we should consider.

Dr. KAUFFMAN. I think from the perspective of the care of children, there are two critical issues: One is to provide the FDA with the regulatory authority to require pediatric studies when it is appropriate; and, second, to deal with the economic disincentives for the industry to be able to afford to develop drug products for children.

Mr. SHAYS. I want to come back to the economic incentives because I am not quite sure what that means, but I would like to just pursue this line.

Ms. Meyers.

Ms. MEYERS. Well, we think that the economic solutions are very important and we are suggesting tax credits for the clinical trials, dollar for dollar, but not to give companies an incentive that is larger than the amount of money that they should be investing in the research to get these things re-labeled.

But there are also some other adjustments that have to be made at FDA to make this a quicker and easier application process.

Mr. SHAYS. So you're talking about not just for secondary use; you're talking in general for all.

Ms. MEYERS. To get any off-label——

Mr. SHAYS. But are you saying—I just want to clarify we are just talking off-label, to be on-label? We are not talking the primary entry into the marketplace?

Ms. MEYERS. No.

Mr. SHAYS. Do you think that needs to be changed there as well?

Ms. MEYERS. No, orphan drugs already get the tax credits and other incentives.

Mr. SHAYS. I wasn't talking about the credits. I'm sorry, I thought you were talking about the regulatory process to be approved on the label.

Ms. MEYERS. I think FDA has been doing an excellent job on getting new drugs approved very, very quickly for serious and life-threatening diseases in the last year or two. And I would rather that we continue to have the FDA be the gold standard for the rest of the world. We are not willing to sacrifice safety or efficacy to get a drug on the market.

Mr. SHAYS. I need to clarify because I thought you had two points: one, you needed the economic incentives; and I thought the second was you needed reform of the process to be approved.

Ms. MEYERS. Of the supplemental NDA process.

Mr. SHAYS. OK. Explain that a little bit better.

Ms. MEYERS. I think FDA should look at the amount of information that they already have on a drug that has been on the market for a period of time and make some choices. For example, perhaps they could pass a rule that says only one well-controlled clinical trial might be needed on a drug that has been on the market for some time and a great deal is already known about it.

Those types of options need to be looked at to make it an easier process so that companies aren't worried about putting so many people from their regulatory affairs staff aside for so many months just to create the application.

Mr. SHAYS. OK. Dr. Kennedy, the issue of positive steps that would make a contribution toward improving the system, what would they be?

Mr. KENNEDY. Well, I think we are talking really three different points here. One is if our objective is to get information on drugs to patients, information to physicians and drugs to patients as expeditiously as possible, we can do that by loosening up on the dissemination of information in considering it an education.

One of the proposals that has been made was to have the inclusion of these unapproved uses provided for in the package insert with the approved uses, very clearly identified that these are unapproved uses for which the drug has been found useful. In looking at what Ms. Meyers was talking about with hydroxyurea, that would be something that could be very easily accomplished. It would provide the information to the physician so that he could make the correct choice as to whether or not his patient fit that.

The supplemental review process, I think I have already provided for that in my testimony. And as far as pediatric use is concerned, one thing that has not come out in testimony this morning is the current procedures that are required to get approval for a drug in children in pediatric use.

Mr. SHAYS. What I don't understand—and we will get to your economic incentive. And let me have you respond to that and then let me just ask the next question. You said economic incentives were important. What would they be?

Dr. KAUFFMAN. Well, may I give you a little background?

Mr. SHAYS. Sure.

Dr. KAUFFMAN. The fact of life is that for most drugs the use in pediatrics or the market in pediatrics is fairly small relative to the adult population, so that the incremental market to spend the resources to get the SNDA for pediatric indication doesn't pay.

Mr. SHAYS. So, it is almost the same problem that rare diseases have?

Dr. KAUFFMAN. Well, to an extent, it is because in its simplest form it can be stated that the marketplace isn't large enough to carry the load for the investment to develop the indication.

Mr. SHAYS. That is a surprising statistic.

Dr. KAUFFMAN. That is reality in our world for most drugs. But for vaccines, for antibiotics, for example, the marketplace is fairly large in children because they tend to have infectious diseases more than any other type of disease, so the marketplace is there. And because of that, antibiotics typically are studied and developed for use and labeled for children.

But when you start looking at gastrointestinal drugs and drugs for kidney disease and drugs for high blood pressure and drugs for asthma and drugs for pain and drugs for anesthetics and so forth, they don't get labeled for children and infants typically because the incremental market isn't there to justify the investment.

Mr. SHAYS. Your point is, it is the same challenge that you have for rare diseases.

Dr. KAUFFMAN. So our position has been that somehow we need to address that economic disincentive by giving the company an incentive to be able to afford to develop it for children.

Mr. SHAYS. It is just kind of fascinating how, when the Government sets up rules and regulations, that the marketplace finds ways to adjust to the system. I'm getting the sense that the secondary use is the safety valve. It is compensating for the problem we have of getting drugs in primary approval. I mean, that is the way it strikes me.

So, I am going to put basically pediatrics and rare diseases in the same economic challenge and I am going to put cancer in a different one. I realize we don't have our witness there, but that is where there is not a cure and so I am going to look everywhere to find one.

Ms. MEYERS. I mentioned, Congressman, before you came in that there are approximately 200 different types of cancer and there are only 4 or 5 of them that are prevalent. The rest are rare. They all fit under the definition of an orphan disease. This entire problem is really an orphan problem, whether it is children as orphans, or cancer, or disease by disease, or all of them together.

Mr. SHAYS. Most cancers become an orphan problem?

Ms. MEYERS. That's right.

Mr. SHAYS. Interesting.

Ms. MEYERS. Yes.

Mr. SHAYS. You are the only witness who represents the pharmaceutical industry here in terms of your presentation. When you heard the dialog taking place between the first two panels and the committee, what was your reaction? How did that relate to your perspective?

Mr. KENNEDY. Well, I thought there was a lot of truth in it, but there were a couple of misconceptions that kept coming through. One is the misconception that if a company goes and gets approval for a primary indication that there is no incentive—and they are allowed to disseminate information on other uses—that there is no incentive for them to pursue research. And that is certainly not the case.

Mr. SHAYS. No incentive to be labeled—research to have secondary applications?

Mr. KENNEDY. Absolutely. And there are two sides of that argument. One is with the ability or with the information available that it is useful or has been tried and without that information.

Let me go to the first one. As a drug goes through the development process, there are a series of activities that are laid out to get these secondary indications. And as you monitor the success of the drug in the marketplace, every time a new supplemental indication is approved, the use becomes wider. So that if we already

had that particular marketplace, we would not see that type of bulge.

The statement has also been made that there is a disincentive to pursue additional indications at the end of a patent expiration. The sad but true fact of life is that the same standard equation applies to loss of market share at the end of patent life whether you've got one indication or whether you've got 20 indications. And economics says that you want to build that base as large as possible so that when you only have half of it you are maximizing your activities.

The third piece comes back to the incentive of companies to pursue additional indications. I can speak from personal experience when in 1989 we had a drug that was approved that had a statement in it that it was not indicated for use in certain neurological disorders. That was a significant incentive for us to do the work and remove that statement from the package insert.

I assume that other manufacturers would have similar motivation if dissemination of information allowed for a statement in the package insert that said the following are not indicated but they have been found to be—there has been information found to be useful.

Mr. SHAYS. It is such a strange term for me to get used to, "indicated." I come back from some of these hearings that I have, these technical hearings, and I talk in front of my staff for a second, and I'm not making sense to them. It is a funny term. How did the term "indication" derive? It doesn't seem funny to you, so it's a dumb question. Forget it. For me, it's a very strange term.

Mr. KENNEDY. You would prefer approved for use?

Mr. SHAYS. No, you use the term "indication."

Mr. KENNEDY. Yes.

Mr. SHAYS. And indication defined how?

Ms. MEYERS. A disease.

Mr. SHAYS. It's a disease.

Mr. KENNEDY. For use in a particular disease, yes.

Mr. SHAYS. But why don't we call it disease?

Mr. KENNEDY. Those of us who deal in the industry are guided by FDA jargon, and that is how it is defined.

Mr. SHAYS. But we are going to give the FDA an opportunity to defend itself on indication.

If you want to pick one question, you've got one question here. In fact, I am going to let my staff member ask all three questions. For our record, we would like these questions. And it is just an indication I didn't do my job well enough.

Ms. FINLEY. What actions has the pharmaceutical industry taken, Dr. Kennedy, to update the labels of products where the manufacturers are aware of extensive off-label use?

Mr. KENNEDY. Currently, the only option that is available to us is to provide for supplemental indications, file for those, discuss them with the FDA, and proceed to obtain them in any way we can, either through doing the studies or using literature citations, if allowed by the agency.

Ms. FINLEY. If the use in rare disease, cancer, and pediatric indications is 80 to 100 percent, as our other witnesses have testified, clearly there must be some recognition on the part of the pharma-

ceutical manufacturers that those products are extensively used. If the companies aren't, as FDA testified, coming in with supplemental NDA's, what is the proper role for the industry in that kind of a situation?

Mr. KENNEDY. The industry is aware of the outside use. Surprisingly, it doesn't come in—I can only speak for my company. It doesn't come in to a significant degree to any type of market projections. It does come in to respect for stocking. You know, we certainly don't want to have a drug that is going to be used for a lot of off-label purposes and not have it available for its initial indication.

Ms. FINLEY. In your opinion, what is the appropriate role of off-label promotion in pediatric, rare disease, and oncology situations?

Mr. KENNEDY. Our position has been very clear and we feel promotion doesn't have a role. Education has a very significant role in providing the information to the physicians and the patients.

Ms. FINLEY. Would the other witnesses care to comment on that?

Ms. MEYERS. Well, I think that the testimony we had from the physician who just left indicates that oncologists, in particular, have to keep up with the medical literature. And they do keep up with the medical literature. They read these journals.

I don't think that there is an issue. If doctors are reading the medical journals, they are finding out this information without a salesmen having to put it in front of their face. If you are treating a rare type of cancer and you want to find out what is the very latest treatment advance, you are going to find out the latest from reading the latest journals.

So the question is promotion: whether a salesman has the right to go into a doctor's office and try to bring his attention to that drug and try to sell it to him for an off-label use or whether they freely can give the information when a physician asks for it.

Right now what the law says is, if the doctor asks for the information, he can be given the information by the pharmaceutical company. But the pharmaceutical company cannot go in there and market the off-label use of a drug to the doctor without the invitation. And that is the way it should stay.

Ms. FINLEY. Dr. Kauffman.

Dr. KAUFFMAN. I think it is important to recognize that physicians access this information through multiple sources, and availability from a sponsor of a drug product is only one of many sources. There are authoritative compendia out there that we all have on our desks which contain information on off-label uses, updated information.

The database from the U.S. Pharmacopeia dispensing information and the AMA drug evaluations is currently being merged and will be available to physicians on CD–ROM as well as hard copy in the near future. This is authoritative, peer-reviewed, annually updated information which contains off-label information if you want to access it there.

The American Hospital Formulary provides the same type of information, and then the current published periodical literature is also available and continuing education courses and so forth.

So we shouldn't be under the misconception that physicians are totally dependent on this source for their education and informa-

tion, but it is one important source. And my only plea would be, if this is done in the future, that the sources that are used to do this are very carefully defined so that we can be sure that only sources that are rigorously peer-reviewed and represent the best in scientific information are used.

Ms. FINLEY. Thank you, Dr. Kauffman. Thank you, Mr. Chairman.

Mr. SHAYS. Thank you. I am happy you asked the questions. Let me say we are all done. I don't know if you all would like to make a comment. I would love to invite the FDA if they would like to come up just to make any observation they would like before we leave. You don't have to defend your concept on indication.

Dr. FRIEDMAN. No, nor will I defend our use of language because that is treacherous as well.

Mr. SHAYS. You didn't create it, did you?

Dr. FRIEDMAN. I would like to just make one very general and simple comment. We very much appreciate the chance to participate in this discussion today. This is a very important issue, as all the different constituencies have spoken in a thoughtful and respectful and sensitive manner, recognizing that no one part of the various interest groups has the whole answer nor is any one part responsible for all the problem, and that by working together we really can achieve something important.

What everybody has said, and what we certainly subscribe to, is that information, good information, is absolutely essential. It is so essential that it should be provided in the easiest, most accessible way. How that is done and how patients can benefit from that is the subject of ongoing discussions that you all have, and we very much appreciate the chance to participate in that, sir.

Thank you.

Mr. SHAYS. Thank you. We look forward to working with the FDA and the other interested parties. This is a very interesting and important issue and we will tread carefully, but we think it is important that we have this dialog and pursue it.

Do any of the three of you wish to make any closing comment? Dr. Kauffman.

Dr. KAUFFMAN. I would just like to say on behalf of the Academy of Pediatrics, we have worked closely over the past several decades with PMA, which is now PhRMA, as well as the FDA to work on this problem of getting drugs labeled for children. During the past 4 or 5 years we have made some major inroads into getting this done. We have a long way to go and we need some help to get the rest of the way.

But I want to commend the FDA as well as PhRMA for their sensitivity to this issue and we will continue to work together to get this done. Thank you.

Mr. SHAYS. Thank you very much. Let me, before closing here, I would just like to recognize our recorder. I had your name down, but for the record your name is?

COURT REPORTER. Donna Ferguson.

Mr. SHAYS. Donna Ferguson, thank you very much. I thank Tom Costa, our clerk, for setting this up and Anne Marie Finley, who has done a yeoman's work in preparing for this hearing, as well as minority counsel and help that we have received.

So thank you, and this hearing is adjourned.

[Whereupon, at 1:45 p.m., the subcommittee was adjourned.]

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