MANAGING THE RISKS FROM MEDICAL PRODUCT USE

CREATING A RISK MANAGEMENT FRAMEWORK

REPORT TO THE FDA COMMISSIONER
FROM THE TASK FORCE ON RISK MANAGEMENT

U.S. Department of Health and Human Services
Food and Drug Administration
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MANAGING THE RISKS FROM MEDICAL PRODUCT USE

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EXECUTIVE SUMMARY

As one of her first initiatives after being sworn in as FDA Commissioner, Dr. Jane Henney established a Task Force to evaluate the system for managing the risks of FDA-approved medical products, focusing particularly on FDA's part in the system. This report is the result of that review.

Briefly, the Task Force assessed risk management practices within the overall healthcare delivery system, focusing on the roles and responsibilities of each participant. The Task Force applied a risk management model used in other Federal sectors. We also examined the various risks from medical products and their sources. The Task Force then evaluated FDA's role in the current system. First, we reviewed the Agency's ***premarketing*** risk assessment and approval processes to determine if serious adverse events are occurring at a higher rate now than they have in the past. Next, the Task Force evaluated FDA's ***postmarketing*** surveillance and risk assessment programs to see if they are doing the job they were intended to do. Finally, the Task Force analyzed all of FDA's risk management activities to evaluate the Agency's role in the overall system for managing medical product risks. Our findings are summarized here.

FINDINGS

The time is right for a new framework

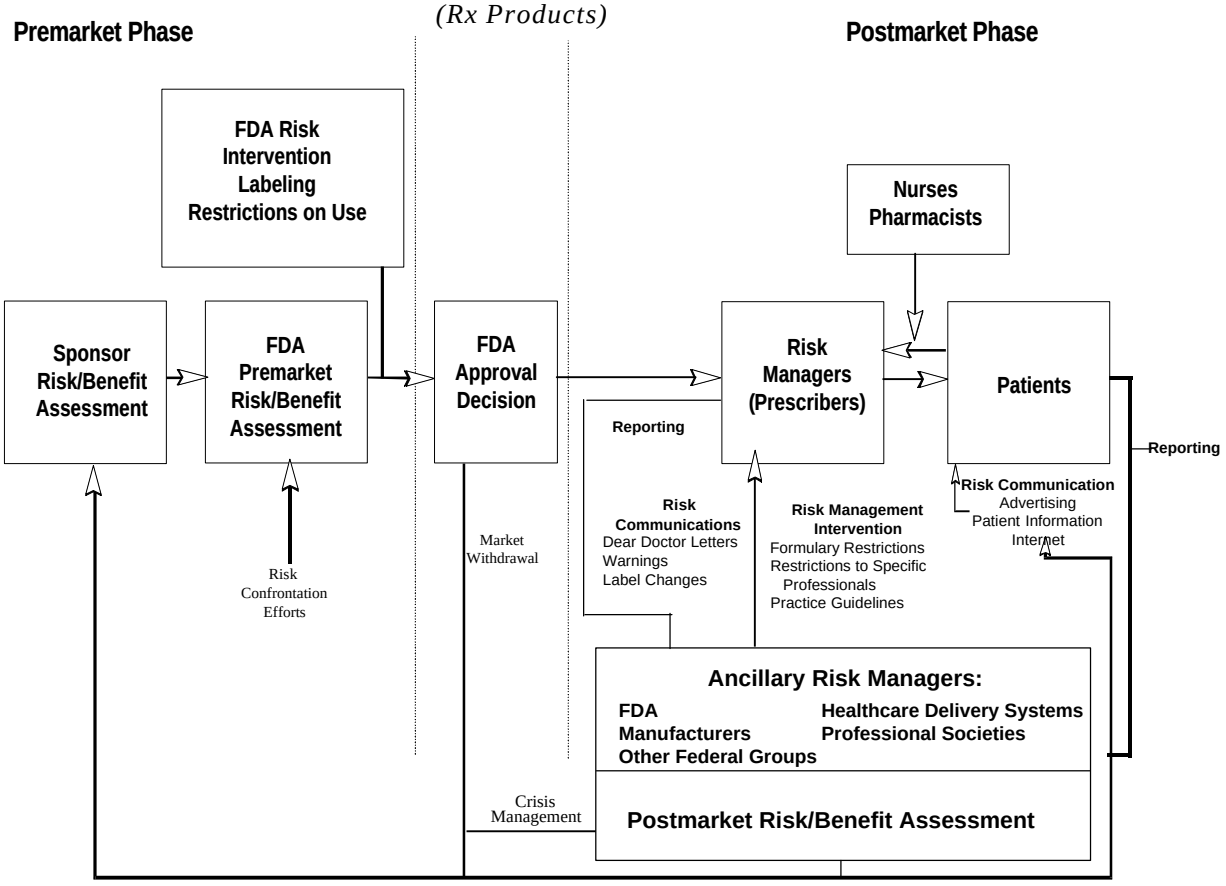
The key finding of our review is that the time is right to apply a systems framework to medical product risk management. The FDA plays only a part in the complex system of risk management. Numerous other groups participate in decision making related to the use of medical products. A systems framework for risk management should enable a better integration of the efforts of all the involved parties. Such a framework also should facilitate a better understanding of both the risks involved in using medical products and the sources of those risks. A better understanding of risks and a more integrated risk management system will enable more effective risk interventions.

The current risk management system has evolved over time

At the turn of this century, healthcare in this country was generally provided by a family practitioner who treated patients from cradle to grave. As illustrated in the following figure, medical products today are developed and used within a complex system involving a number of key participants: (1) manufacturers who develop and test products and submit applications for their approval to the FDA; (2) the FDA, which has an extensive premarketing review and approval process and uses a series of postmarketing surveillance programs to gather data on and assess risks; (3) other participants in the healthcare delivery system, including healthcare practitioners; and (4) patients, who rely on the ability of this complex system to provide them with needed interventions while protecting them from injury.

Complex System for Managing the Risks of Medical Products

(Rx Products)



Not everyone's role is clearly defined

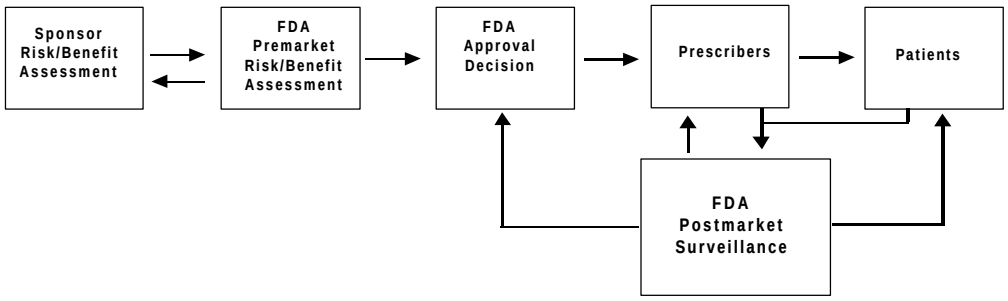
Although medical products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. All participants in the medical product development and delivery system have a role to play in maintaining this benefit-risk balance by making sure that products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk.

In some cases, roles are clearly defined. For example, FDA's current efforts, which are laid out in the Federal Food, Drug, and Cosmetic Act, are largely devoted to pre- and postmarketing risk

assessment. The FDA approval/nonapproval decision is the Agency's central risk management action. FDA must ensure that beneficial medical products are available and labeled with adequate information on their risks and benefits while protecting the public from unsafe products or false claims. The figure below is a snapshot of FDA's role in the current risk management system. During premarketing review, the Agency assesses the evidence demonstrating the benefits and describing the risks of medical products.

FDA Role in Medical Products Risk Management

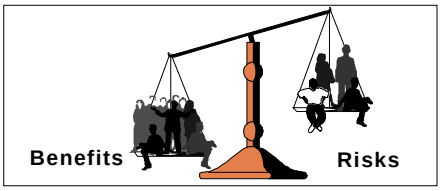
(Rx Products)



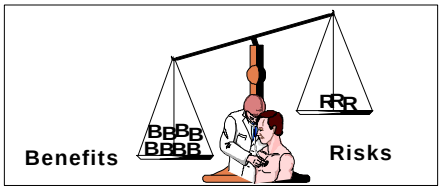
The Agency approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use. A major goal of the premarketing review is to ensure that products are truthfully and adequately labeled for the population and use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk and benefit to the healthcare community and patients.

Once medical products are on the market, however, ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products wisely, thereby minimizing adverse events.

FDA
evaluates benefits/risks for the population



Provider
evaluates benefits/risks for a patient



Patient
evaluates benefits/risks in terms of personal values

To assist with postmarketing risk management, the Agency maintains a system of complex postmarketing surveillance and risk assessment programs to identify adverse events that are not identified during medical product development and premarketing review. FDA monitors suspected adverse events associated with the use of an approved medical product. The Agency uses this information to initiate labeling updates and, on rare occasions, to reevaluate the marketing decision.

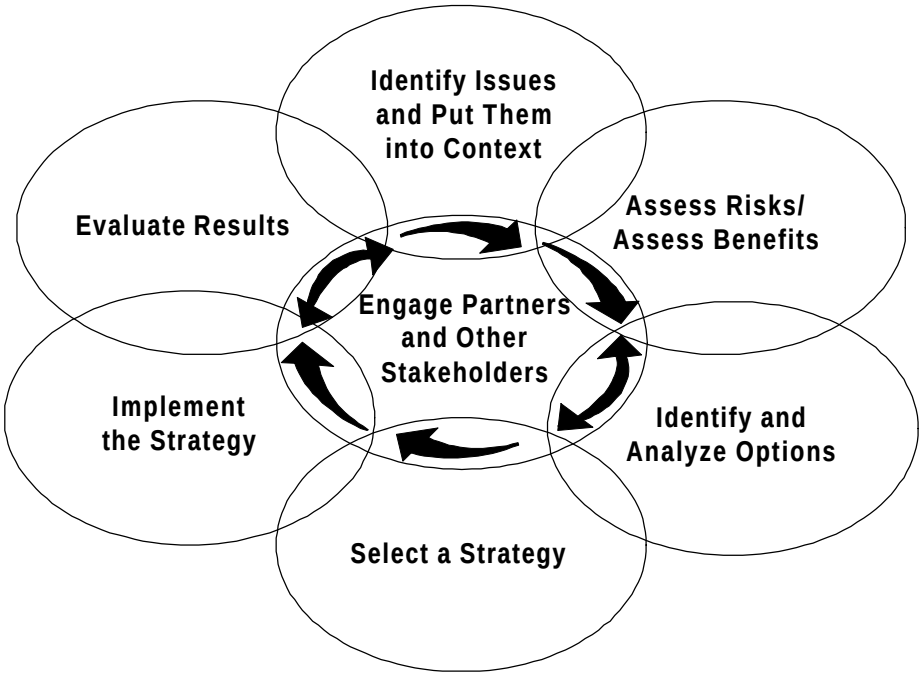
Although the FDA's role is fairly clear, the roles of some of the other participants are less clear. This is because what began as individualized care by one practitioner has evolved into a complex system of risk management that now involves manufacturers, the FDA, practitioners, many other elements of the healthcare delivery system, and patients. With the flood of new products reaching the marketplace, an increasingly complex healthcare environment, and the emerging global market, the Task Force believes that a new conceptual framework for risk management activities is needed. The new framework should help define the roles of those involved and better integrate their efforts.

How would a new systems framework look?

As discussed in Part 4, a specific model has been developed for managing the risks associated with other health and safety issues

within the Federal Government.[1] This model encompasses the basic processes that are used to identify and assess the risks of specific health hazards, implement activities to eliminate or minimize those risks, communicate risk information, and monitor and evaluate the results of the interventions and communications. The Task Force found that the processes identified in the Federal model are consistent with the activities the Agency and many of the other involved participants currently undertake as part of their approach to risk management. Under the current system, however, these activities are fragmented, rather than part of an integrated systems effort. The Task Force easily adapted the Federal model to create a proposed model for managing the risks associated with using medical products. (See the proposed model below.) This new framework encourages a much greater integration of risk management efforts than the current system.

Proposed Risk Management Model



[1] Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management — Final Report*, Vol. 1, 1997.

One activity often missing from other risk management models that is implicit in risk-benefit assessment and is critical in a system that would manage healthcare risks involves engaging healthcare partners and other stakeholders in risk-benefit analyses. This activity is characterized by others as ***risk confrontation***: community-based problem solving that actively involves relevant stakeholders in the decision-making process.[2] This is one area of activity that traditionally has had lower priority in the Agency than its pre- and postmarketing scientific risk assessment responsibilities. The Task Force believes that risk confrontation is a key process that needs to be a part of any new risk management framework.

FDA should engage stakeholders to examine the current risk management system

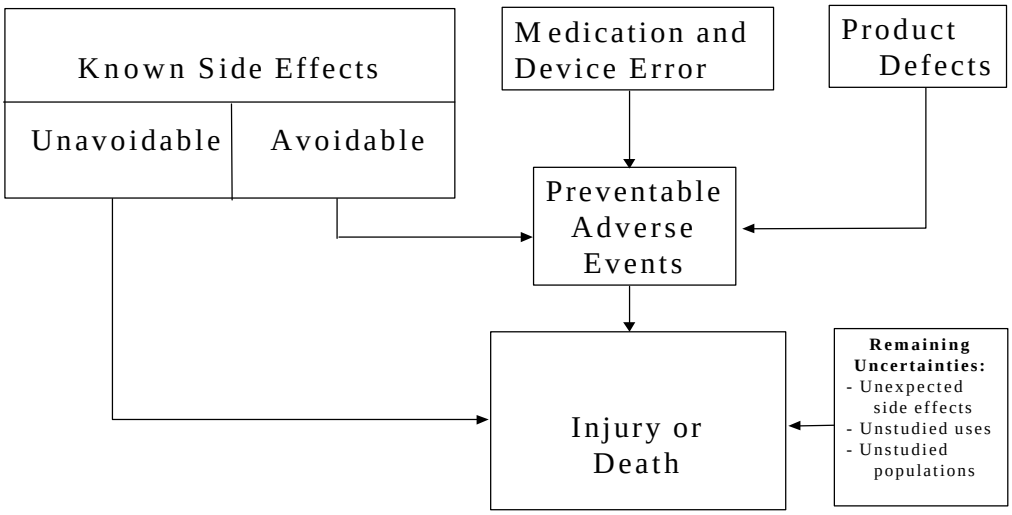
The Task Force recommends that FDA take the opportunity to engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all participants of the risk management system — FDA, industry, healthcare provider organizations, healthcare practitioners, patients, and the public. Only by examining the roles of these various participants can gaps and misallocation of efforts be identified and improvements made.

Understanding the types of risks and their sources is critical

To evaluate the current system, it is critical that the stakeholders also consider what is known about the sources of risk from medical products and what is not yet completely understood. As discussed in detail in Part 1 of the report, risks from medical products generally fall into four categories.

[2] Leviton, L.C., C.E. Needleman, and M.A. Shapiro, *Confronting Public Health Risks: A Decision Maker's Guide*, SAGE Publications, Inc., 1998.

Sources of Risk From Medical Products



Most injuries and deaths associated with the use of medical products result from their ***known side effect***s. Some side effects are unavoidable, but others can be prevented or minimized by careful product choice and use. It is estimated that more than half of the side effects from pharmaceuticals are avoidable.[3] Other sources of preventable adverse events are ***medication or device errors***. Injury from ***product defects*** is unusual in the United States because of the great attention paid to product quality control and quality assurance during manufacturing. The final category of potential risk involves the ***remaining uncertainties*** about a product.

Knowledge about a product will always be limited to some extent at the time of approval by factors in the product development process. For example, rare side effects and long-term outcomes (both positive and negative) may not be known when a product is approved because of the relatively small size and short duration of clinical trials. And because of the populations not studied in clinical trials (e.g., pregnant patients, children, people with other diseases) or minimally studied (e.g., geriatric patients), side effects may be discovered if these groups are treated with a product after it goes

[3] Bates, D.W., L.L. Leape, and S. Petrycki, "Incidence and Preventability of Adverse Drug Events in Hospitalized Adults," *J Gen Intern Med.*, 8:289-294, 1993.

on the market. Even after long use of a product, uncertainties will remain.

One problem for discussion is the lack of adequate data about the causes, incidences, preventability, and relative contribution of the various types of risk. Currently, no group has the role of collecting and analyzing these types of data. Systematic approaches to risk management require the use of such data to plan and evaluate the success of risk interventions. It is unlikely that major improvements in risk management can occur without better data.

All participants in the risk management system, including the FDA, have a role to play in minimizing the risks from using marketed medical products. The Task Force believes that the stakeholders should collaborate to determine how better data on risks can be collected — so that efforts and interventions can be targeted to the most serious problems, and the effects of interventions can be evaluated.

FDA's current role in risk management

Turning to FDA's role in overall risk management, the Task Force examined the Agency's premarketing and postmarketing risk assessment activities, evaluating their quality and effectiveness. The Task Force also looked at FDA's efforts in other aspects of risk management such as risk communication, confrontation, and overall evaluation.

As discussed in detail in Part 2 of this report, the Task Force evaluated whether the heightened sense of time pressure on Agency review teams has reduced the quality of FDA's premarketing reviews or caused poor decision making. We studied how often previously unanticipated serious adverse events[4] were identified after approval in drugs reviewed since the implementation, beginning in 1990, of several legislative (e.g., PDUFA) and managerial initiatives to speed the Agency's review process.[5] We

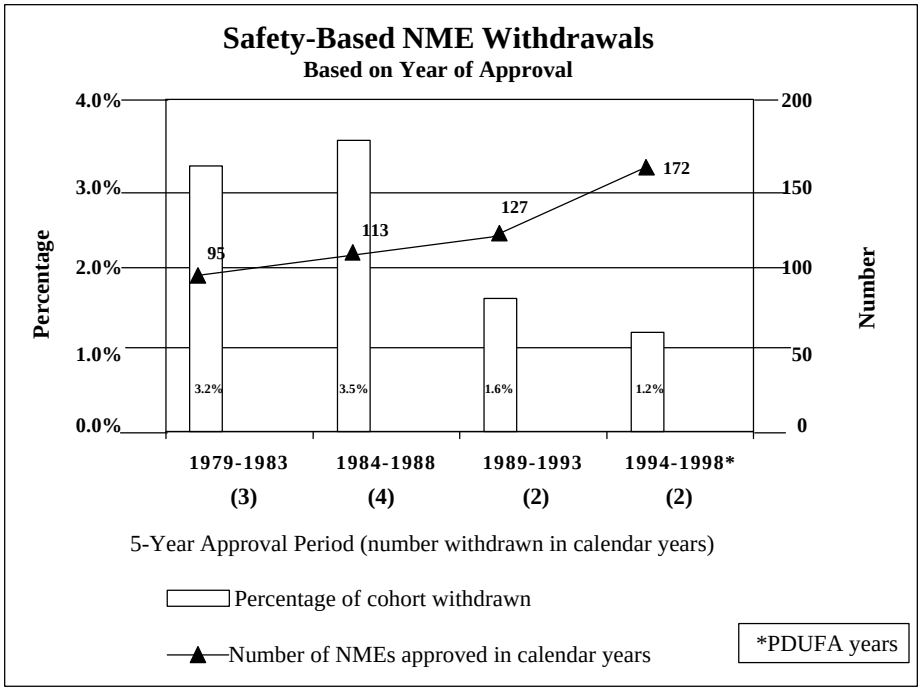
[4] A number of terms are used to describe an adverse event, including *adverse drug reaction* (ADR), *adverse experience*, and *adverse effect*. In this report, the term *adverse event* is used in most cases to avoid confusion.

[5] Through the Prescription Drug User Fee Act of 1992 (PDUFA) and the Food and Drug Administration Modernization Act of 1997, Congress has encouraged the FDA to act more rapidly in making decisions on whether new medical products may enter the marketplace.

then compared the numbers to those collected by a 1990 General Accounting Office (GAO) report on serious adverse events for drugs reviewed prior to 1990.[6] We also examined FDA's quality control systems for premarketing review and marketing decisions to see if adequate systems are in place.

Rates of withdrawals and adverse events remain low

We found that FDA's premarketing review processes are successfully identifying the serious risks associated with using medical products at least as well as in previous decades. Despite shortened FDA review time, comparisons of drugs reviewed and approved during the 1990s to those approved previously show that the rate of market withdrawals for safety reasons has remained relatively unchanged over the decades. As the graph below shows, the rate of safety-based market withdrawals of new molecular entities (NMEs) has ranged from approximately 1 to 3.5 percent over the past several decades.[7]



[6] Government Accounting Office, *FDA Drug Review — Postapproval Risks 1976 - 1985*, GAO/PEMD-90-15, April 1990.

[7] FDA, Center for Drug Evaluation and Research, *1998 Report to the Nation*, May 1999.

With advances in scientific knowledge, safety problems may be identified for long-marketed products. For example, of the five drugs withdrawn for safety reasons after 1992, two were approved before PDUFA was implemented.[8] In addition, comparisons also showed that unexpected serious adverse events resulting in revisions to product labeling after approval are occurring proportionately less often than in the past.

The Task Force also found that the key elements of an International Standards Organization (ISO)-modeled quality assurance/quality control program for premarketing review are in place and being used. FDA has consistently used supervisory rereview, conducted by subject matter experts, for 100 percent of the marketing decisions as the cornerstone of its quality control function. These quality control reviews are conducted typically at three supervisory levels before a final approval decision is made.

Some factors limit the identification of adverse events

The Task Force analysis identified several factors in the medical product development process that limit the Agency's ability to observe some kinds of adverse events before marketing. Factors include the relatively small size and short duration of clinical trials and the representativeness of the patients studied. For example, as discussed in Part 2, rare side effects are often not observed before marketing because of the limited number of patients exposed to a product before approval. And, most trials do not last long enough to enable identification of potential long-term side effects. In addition, patients in clinical trials are often not representative of the types of people who will be exposed to a product once it goes on the market. Changing these aspects of medical product development could increase the manufacturers' and the Agency's ability to identify serious risks before marketing. However, such changes would increase development costs and slow product availability.

Finally, the Task Force believes that in the case of some new medical products, consideration should be given to how rapidly they are made available in the marketplace for widespread use. Slowing a rapid market rollout for some products when time-tested

[8] Redux, Pondimin, Seldane, Duract, and Posicor were withdrawn from the market in 1997 and 1998; Seldane and Pondimin were approved prior to PDUFA. For a full discussion, see, Friedman et al., "The Safety of Newly Approved Medicines," *JAMA*, Vol. 281, No. 18, May 12, 1999.

alternatives are available could limit the impact of unexpected serious adverse events.

Postmarketing surveillance and risk assessment are performing as designed

We found that the postmarketing surveillance programs currently in place are good at rapidly detecting most unexpected serious adverse events that occur during the postmarketing period. As described in more detail in Part 3 of this report, the Agency relies principally on a ***passive*** adverse event reporting system, depending to a great extent on voluntary reporting by the healthcare community. The system rapidly alerts the Agency to the occurrence of rare, serious adverse events not previously identified.

The system also provides an increased understanding of the range of severity in known product-associated adverse side effects. We found that the Agency's postmarketing surveillance and risk assessment programs are performing well for the goals they were designed to achieve. However, FDA's programs were not designed to evaluate the rate, or the impact, of known adverse events.

The Task Force has presented some options for expanding the use of automated systems for reporting, monitoring, and evaluating adverse events and product defects and increasing the Agency's access to data sources that would supplement and extend its passive reporting systems. These would enhance the Agency's ability to evaluate reports of serious adverse events. Examples of such sources include broad-based health information databases and data from sentinel user facilities where staff are trained to rapidly recognize and accurately report adverse events. Implementing some of these changes would require increased funding.

CONCLUSIONS, RECOMMENDATIONS, AND OPTIONS

Conclusions

Medical products provide great benefit to the public, but they can also cause injury. FDA and the many other participants in healthcare delivery act to maximize the benefits and minimize the risks associated with using medical products, but often the actions of the participants are insufficiently integrated. The Task Force believes that the common goal of maximizing benefits and

minimizing risks could be greatly advanced if the participants in the system worked together to gain an understanding of these activities within a systems framework. To achieve such a framework, we need a better understanding of the risks involved and their sources, and we need to clarify our individual roles and ensure that our individual roles are well integrated. Only then can we plan effective risk management strategies.

The Task Force also examined in detail FDA's role in the overall system. We find that the Agency's pre- and postmarketing risk assessment systems are performing well. Nonetheless, we believe that additional emphasis should be placed on the quality assurance of our premarketing review programs. In addition, the Task Force finds that program expansion is needed to ensure that our postmarketing programs are able to meet the challenges of the current regulatory and healthcare environment.

Recommendations

The Task Force is making a number of recommendations as a result of its review. Most recommendations center around ways that FDA, within the confines of the current system, can further improve its risk management activities. The Agency intends to implement these recommendations. Many of these improvements already are underway, and the Task Force recommends that ongoing enhancements be aggressively pursued. Specifics can be found at the end of Parts 2, 3, and 4 of the report, but these recommendations generally include:

- Initiate steps to have each Center establish separate quality assurance/quality control units.
- Ensure and document ongoing professional education and core competency training for all reviewers.
- Complete the good review practice documents and keep them current.
- Rapidly complete AERS and enhance MAUDE adverse event reporting systems for pharmaceutical products and medical devices.
- Integrate existing postmarketing systems so analytical tools, data entry, and editing can be uniformly applied, and all

information is readily available to every reviewer.

- Enhance and intensify surveillance of newly marketed products.

- Develop new methodological tools for inference from available datasets.

The Task Force also identified a number of options for consideration, which, if adopted, might contribute to improved risk management. These ideas need full public policy analysis and review to understand their potential value, costs, and acceptability to the various stakeholders in medical product risk management. Some of the options would require significant new resources and legislative changes. Input from stakeholders on these options and their prioritization is needed. For these reasons, the Task Force's key recommendation is that:

- FDA join in or convene a meeting, or series of meetings, with stakeholders to discuss the current system for managing risks. As part of this meeting, FDA should consult stakeholders about the options identified in detail in the report and summarized below.

Options

The Task Force identified a number of options that we believe may improve the FDA's risk management activities as well as improve the overall system of managing the risks from medical products. These options should be evaluated in the context of the stakeholder risk confrontation meeting(s) recommended above. Only by working with all other participants in the overall risk management system for medical products can the Agency arrive at the most effective approach for managing those risks.

Details of the options for public consideration can be found in the relevant chapters of this report. In summary, these options might include:

- Examine and evaluate mechanisms designed to address the inherent limits of premarketing development (e.g., wider use of large, community-based simple trials, restricting exposure during the early postmarketing period).

- Design and implement additional mechanisms to obtain

postmarketing information (e.g., sentinel sites, prospective product use registries, enhanced links to external databases).

- Enhance Agency epidemiological and methodological research activities.

- Enhance the Agency's role and responsibilities in risk communication.

- Increase the number of postmarketing risk interventions for products with special risks, such as restricting distribution of products or requiring mandatory educational programs for healthcare professionals and patients.

- Seek legislative changes for other types of risk intervention, such as suspension authority for drugs.

INTRODUCTION

As set forth by Congress in section 406 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act), the mission of the U.S. Food and Drug Administration (FDA) is, in part, to (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate and timely action on the marketing of regulated products and (2) protect the public health by ensuring that human drugs, including biologics, are safe and effective and that there is reasonable assurance of the safety and effectiveness of medical devices intended for human use. FDA is charged with pursuing this mission through consultation with experts in science, medicine, and public health, and through cooperation with consumers, users, and industry. The Modernization Act also instructs FDA to maximize the availability and clarity of information concerning new products for consumers and patients.

During the 1980s and the early 1990s, critics talked of a *drug lag* in the United States. They claimed that long review times were denying the American public the benefits of new products that were available in other developed nations many months or years earlier.

LEGISLATIVE AND MANAGEMENT INITIATIVES HAVE HELPED SPEED REVIEW TIME

To address concerns about the timeliness of reviews, the pharmaceutical industry, consumer groups, FDA, and Congress worked together to develop new legislation. Through the Prescription Drug User Fee Act of 1992 (PDUFA) and the Modernization Act of 1997, Congress has encouraged the FDA to

act more rapidly in making decisions on whether new medical products may enter the marketplace. PDUFA provides FDA with additional funds from user fees, permitting FDA to employ a larger workforce to handle review workloads. The fees are paid by the sponsors of new drug and biological products and can only be used in support of the new pharmaceutical product review process. PDUFA did not change FDA's standard for drug and biologics safety and effectiveness.

These legislative initiatives have been successful. Since its enactment, PDUFA user fees have paid for a 60-percent increase in staff assigned to the review of new pharmaceutical applications. The average time from submission of an application to approval has dropped from about 30 to 12 months. Along with this improvement in review times has come an increase of almost 40 percent in the number of new products approved per year, from an average of 70 to 97 applications per year. Industry negotiated strict administrative accountability and aggressive review time performance goals in exchange for its support of PDUFA. FDA has established an excellent record of meeting, or exceeding, these goals. FDA's faster review is not just the result of more FDA staff, but is also due to improvements in program management and efforts to streamline the review process.

Unlike the Center for Drugs and the Center for Biologics, the Center for Devices did not benefit from user fees. However, the medical device program received a budget increase in 1994. This increase, along with a reallocation of funds from other activities, management changes, and program reengineering improved results for the device program. For example, the review time for device premarket applications (PMAs) has decreased from 27 months in 1994 to 12 months in 1998.

CONCERNS HAVE BEEN RAISED ABOUT THE EFFECTS OF PDUFA

In the late 1990s, Public Citizen's Health Research Group and others began to express the concern that PDUFA's focus on shortening the review time has altered relationships among FDA's reviewers, FDA management, and the regulated industry. Critics have charged that time pressures resulting from PDUFA have led to a decrease in the quality of FDA reviews. To investigate this possibility, Public Citizen conducted a survey of FDA reviewers. Of a total of 172 surveys mailed, 53 responses were received. Nineteen medical officers reported that their recommendations to

disapprove a product had not been followed. Although the survey design did not allow the collection of information on *how frequently* this had occurred, *when* these specific reviews had been conducted, or *how many* reviews had been conducted by each survey respondent, the survey nonetheless raised a serious charge: Pressures to speed reviews, pressures to approve, and scientific disagreements among reviewers and managers have reduced the quality of FDA reviews, resulting in poor decisions that, in turn, have led to an increase in unanticipated adverse events.

The ensuing public discussion has highlighted the fact that medical products are not 100 percent safe, and even after extensive evaluation, products are not always fully understood. It is widely accepted that enormous benefits can be gained from using medical products. Yet, while most are well tolerated, producing only minimal side effects or rare adverse events, some products can be very toxic, producing a high rate of complications from side effects. It is estimated that millions of adverse events associated with the use of medical products occur each year; many of these are serious, and many result in death.[1]

Recent increased scientific and media attention to serious adverse events resulting from the use of medical products has raised questions about the risks associated with the use of those products. Medical product quality has not been the focus of concerns.[2] Concerns have focused on serious adverse events resulting from the use of medical products after the products are on the market. And, although many participants are involved in managing the risks from medical product use, when serious adverse events do occur, the public often turns to the FDA for answers.

THE COMMISSIONER ASKED THE TASK FORCE TO LOOK INTO PUBLIC CONCERNS ABOUT THE RISK MANAGEMENT SYSTEM

As one of her first initiatives after being sworn in as FDA Commissioner, Dr. Jane Henney created a Task Force to examine the current system to manage the risks associated with using

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[1] Lazarou, J., B.H. Pomeranz, and P.N. Corey, "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies," *JAMA*, 279:1200-1205, 1998.

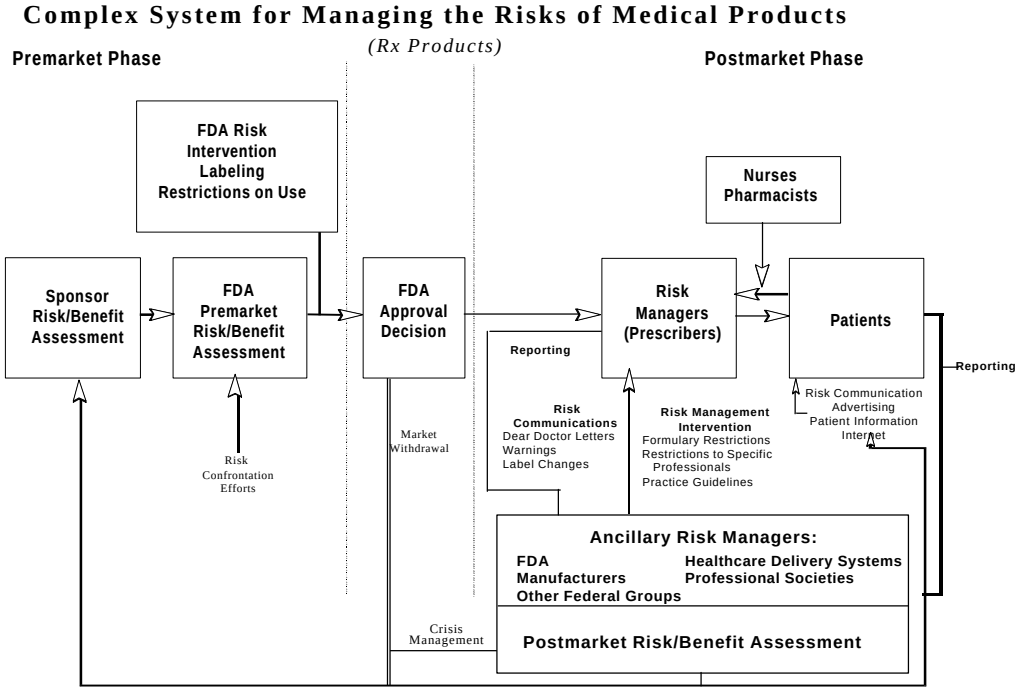
[2] Although FDA devotes great attention to regulating the quality of medical products, this report does not address product quality problems.

medical products. She asked the Task Force to try to identify the strengths and weaknesses in the overall system, and to review FDA's role in the system. With regard to the Agency's role, the Commissioner asked the Task Force to concentrate its review in three basic areas: (1) the quality of the Agency's premarketing review and risk assessment, (2) the strengths and weaknesses of the Agency's postmarketing surveillance and risk assessment, and (3) other FDA risk assessment activities.

Part 1 of this report provides a general discussion of the risks involved in medical product use and an overview of the risk management system and FDA's role in that system. Parts 2 and 3 discuss the Agency's premarketing and postmarketing risk assessment activities. Part 4 takes a broad look at the overall risk management system and makes recommendations for creating a new systems model.

PART 1: BACKGROUND — WHAT ARE THE RISKS AND WHAT IS FDA'S ROLE IN MANAGING RISK?

At the turn of this century, healthcare was generally provided by a family practitioner who treated patients from cradle to grave. Today's healthcare products are developed and used within a complex system involving a number of key participants. As illustrated in the following figure, participants include (1) manufacturers who develop and test products and submit applications for their approval to the FDA; (2) the FDA, which has an extensive premarketing review and approval process and uses a series of postmarketing surveillance programs to gather data on and assess risks; (3) the healthcare delivery system, including its many elements; and (4) patients, who rely on the ability of this complex system to provide them with needed interventions while protecting them from injury. In many cases, the roles of the participants in this system evolved independently, and in some cases, the roles are not clearly defined.



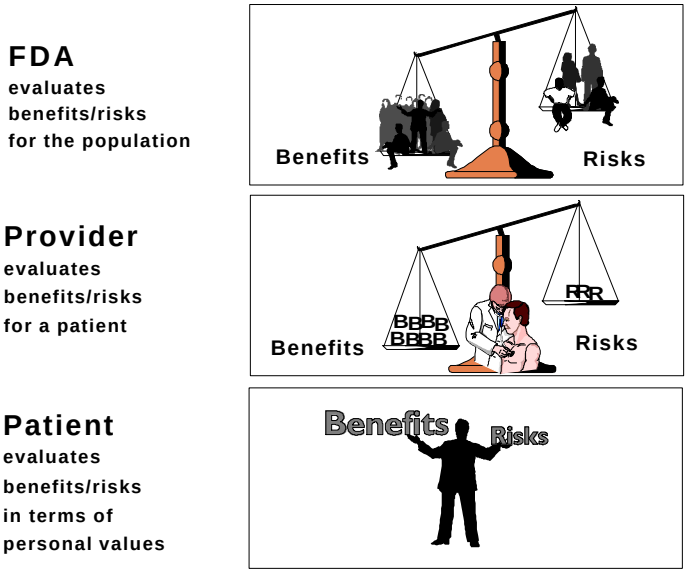
GOALS ARE TO MAXIMIZE BENEFIT, MINIMIZE RISK

The choice to use a drug, biological product, or device involves balancing the benefits to be gained with the potential risks of using a product. As illustrated above, an elaborate system has developed in the United States with the goals of maximizing the benefits and minimizing the risks associated with using medical products. Under this system, medical products must undergo FDA approval before marketing. FDA's premarketing review involves (1) developing criteria for the evidence of product safety and effectiveness that manufacturers must submit to FDA, and (2) evaluating the data manufacturers submit to see if the product meets the statutory standard for market approval. Briefly, the system works as follows. After a systematic development process that includes clinical trials, the manufacturer submits an application to the FDA for approval. After a thorough review of the data, FDA makes a decision to approve or not approve a product to treat a specific condition, based on a benefit-risk analysis for the intended population and use. Although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with risks. A *safe medical product* is one that has

reasonable risks, given the magnitude of the benefit expected and the alternatives available.

One result of FDA's premarketing evaluation of a new product is the approval of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's potential adverse side effects, and explain how the product should be used to maximize benefits and minimize adverse side effects.

Once approved, products move swiftly into the marketplace for use by prescribers and patients. As shown in the next figure on balancing risks and benefits, after FDA evaluates the risks and benefits for the population, the prescriber is central to managing risks and benefits for the individual. In addition, patients make decisions about treatment choices based on their personal valuation of benefits and risks. In the context of an individual treatment decision, FDA's role in reducing risk involves ensuring that accurate, substantiated, and balanced information about a product is available to the prescriber and the patient. This system, when functioning well, succeeds in managing a balance between benefit and risk. But FDA's mission to ensure the safety of medical products cannot be accomplished without effective partnerships with healthcare practitioners and the public.



FDA also operates postmarketing surveillance programs intended to identify unexpected risks of approved products. When new risks

are identified in a medical product, the manufacturer adds them to the labeling, or, if serious enough, they may trigger an Agency reevaluation of the approval decision.

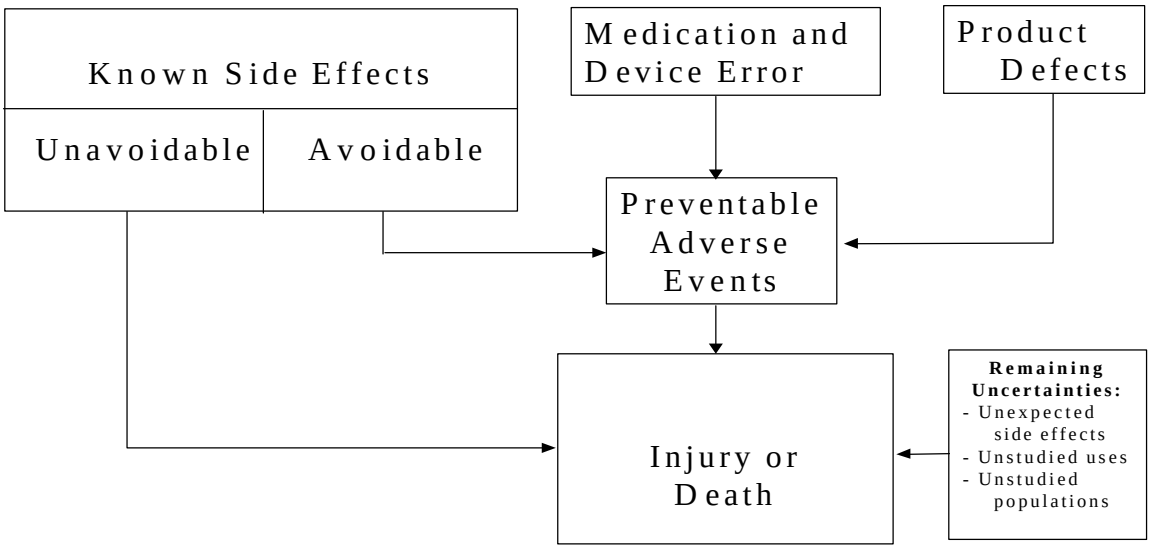
Recent concerns about the safety of medical products have focused on several types of risks. For newly approved products, concerns have centered on unanticipated side effects that emerge after a product is on the market. In addition, concerns have been raised about FDA's ability to ensure the appropriate use of regulated products in medical practice. For example, how far should the Agency intrude into traditional areas of medical practice when the safe use of a product requires practitioner training, or frequent patient blood testing? Is the Agency responsible when a medical product is used beyond the parameters of the approved labeling? Some reports have focused on the human and economic costs of medication errors, while others are concerned about serious adverse events that have occurred even when a medical product has been used appropriately. Because each of these types of risks has a different source, effective management of each is likely to be different. To understand the complexity of managing the risks associated with using medical products, it is important to understand the different types of risks and their sources.

WHAT *ARE* THE RISKS INVOLVED WITH USING MEDICAL PRODUCTS?

In general, the sources of medical product risks can be thought of as falling into the following four categories: (1) product defects, (2) known side effects, both avoidable and unavoidable, (3) medication or device errors, and (4) remaining uncertainties. When using a medical product results in a patient's serious injury or death, the patient is said to experience a serious adverse event.[1]

[1] A number of terms are used to describe an adverse event, including *adverse drug reaction* (ADR), *adverse experience*, and *adverse effect*. For the purposes of this report, the term *adverse event* is used in most cases to avoid confusion.

Sources of Risk From Medical Products



Product defects

Historically, product defects have been an important source of medical product-associated injuries. A significant portion of FDA's resources are currently devoted to regulating product quality. Although additional resources are needed to maintain and enhance current oversight activities, the risks associated with defective medical products are relatively well managed.[2] FDA research, surveillance, and inspections form the cornerstone of FDA efforts to keep product defects to a minimum. The risks associated with poor product quality are not the subject of this report.

Known side effects

When using a drug or other medical product, a patient runs the risk of experiencing reactions resulting from the product's interaction with the body. For pharmaceuticals, these reactions are commonly termed *side effects.* They usually have been identified and are indicated as possible risks in a product's labeling. Known side effects are the source of the majority of injuries and deaths resulting

[2] For example, for pharmaceuticals, very few injuries or deaths occur as a result of product defects.

from product use.

During product development and the premarketing review process, manufacturers and the FDA focus on identifying and understanding this very large category of risks. The risks must be identified, described, and measured before a sound overall risk-benefit decision can be made on the product's approval. After approval, product labels describe how to select patients, how to select and modify the dose schedule, how to avoid interacting treatments, how to monitor for toxicity, and what measures to use to avoid or mitigate toxicity. If additional side effects are identified during the postmarketing phase, the manufacturer changes the product's labeling information to reflect these possible side effects.

Avoidable side effects

Some known side effects are predictable and avoidable. To avoid them, the healthcare practitioner must select the best treatment and plan appropriate measures to manage the risks, for example, patient hydration for products that are toxic to the kidneys, or dose adjustments for patients with impaired kidney function. A medical practitioner can choose the wrong therapy for a specific condition (for example, using antibiotics for viral infections). Alternatively, a practitioner may prescribe the appropriate therapy, but fail to individualize the therapy or monitor the patient for signs of toxicity. Examples of avoidable side effects include the consequences of known drug-drug interactions or side effects caused by prescribing an inappropriate dosage in the elderly. Communicating the potential for these types of risks to healthcare practitioners and explaining how to minimize them are major goals of product labeling. Occasionally, to further reduce such risks, additional restrictions are placed on the use of a product, its availability, or its promotion. But, generally, existing regulatory controls are intended to provide the necessary information to the product users and rely on them to use the product safely.

Problems resulting from poor product selection by a practitioner can be reduced by interventions such as targeted medical education, but are largely not amenable to FDA action. Reducing the risks related to poor product use requires collaboration by the manufacturer, the FDA, healthcare professionals, the various components of the healthcare delivery system, and patients.

Unavoidable side effects

In many cases, known side effects are unavoidable, even with the

best medical practice because they can occur even when a product is used appropriately. Although estimates vary, the overall human and economic costs of unavoidable side effects are high.[3] The risk of experiencing such side effects is the inevitable price for gaining the benefits of treatment. Superinfection following antimicrobial chemotherapy, fatigue and depression from interferon use, and bone marrow suppression from chemotherapy are common, predictable, and usually unavoidable side effects. Successfully managing these risks centers on ensuring that both the practitioner and patient are fully aware of the risks involved in treatment and that the patient is carefully monitored.

Medication or device errors

Medication or device errors involve the incorrect administration of the prescribed product or incorrect operation or placement of a medical device. Errors also can involve the unintended substitution of the wrong product for the prescribed product. Errors arise, for example, when a confusing product name results in the wrong product being dispensed, or when inattention results in an overdose of an intended drug. Substantial numbers of injuries and deaths occur annually from medication or device errors.[4] In general, these errors are believed by experts to result from systemic problems, rather than from a single individual's mistake. Such errors are not totally preventable, but can be minimized through interventions to the system.

Many outside organizations are involved with identifying and reducing medication errors. In its final report, The President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry called on interested parties to jointly develop a healthcare error reporting system to identify errors and prevent their recurrence. As a result, the Quality Interagency Coordination (QuIC) committee was formed on March 13, 1998. In addition,

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[3] Johnson, J.A., and J.L. Bootman, "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model," *Arch Intern Med.*, 155:1949-1956, 1995. See also Bates, D.W., N. Spell, D.J. Cullen et al., "The Costs of Adverse Drug Events in Hospitalized Patients," *JAMA*, 277:307-311, 1997.

[4] Bates, D.W., D.J. Cullen, N. Laird et al., "Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention," *JAMA*, 274:29-34, 1994. See also Bates, D.W., N. Spell, D.J. Cullen et al., "The Costs of Adverse Drug Events in Hospitalized Patients," *JAMA*, 277:307-311, 1997; and Johnson, J.A., and J.L. Bootman, "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model," *Arch Intern Med.*, 155:1949-1956, 1995.

The Institute of Medicine within the National Academy of Sciences is expected to issue a report in 1999 on preventing medication errors.

In light of a series of highly publicized major adverse events in hospitals during 1995, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) reexamined existing processes for evaluating and monitoring such events and established a more consistent approach to reducing the likelihood of medication errors in all types of healthcare organizations. By 1996, JCAHO had established a sentinel event reporting policy that would provide for (1) a safe harbor context to encourage the self-reporting of sentinel events, (2) the establishment of a database of such serious events to determine their demographics and epidemiology, (3) the sharing of this aggregate information among healthcare organizations, (4) the continuous development and dissemination of information about the sentinel event causality through root cause analysis, and (5) an emphasis on the concept of prospective systems analysis to minimize errors and protect against the effects of errors through improved design and redesign of healthcare processes and systems.

In 1995, a National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) was formed. The NCC MERP is a collaborative effort to (1) increase awareness of medication errors and methods of prevention; (2) stimulate reporting to a national system for review, analysis, and development of recommendations to reduce and prevent medication errors; (3) stimulate the development and use of a medication error reporting and evaluation system; (4) to examine and evaluate the causes of medication errors; and (5) to develop strategies relative to system modifications.

In 1997, the American Medical Association (AMA) announced the formation of the National Patient Safety Foundation (NPSF). The NPSF is a collaborative effort in pursuit of three goals: (1) serve as an educational forum for building awareness among providers and the public about patient safety, errors in healthcare, and preventive strategies; (2) support new research designed to analyze risk factors in healthcare to develop practical tools and solutions; and (3) serve as a clearinghouse for research information, best practices protocols, and preventive tools regarding patient safety risk factors.

In December of 1997, the Health Care Financing Administration (HCFA) proposed “Conditions of Participation in Medicare and

Medicaid" that would require hospitals to routinely monitor for adverse drug events and medication errors.

The Institute for Safe Medication Practices and the United States Pharmacopeia (USP), operate a voluntary medication error reporting system (MERS). In addition, the USP has recently introduced MedMARx, an Internet-accessible database software program designed to anonymously report, track, and benchmark medication error data in a standardized format for hospitals nationwide.

During the premarketing review process, FDA works to reduce the risk of medication and device errors by evaluating product design and packaging, reviewing product names, and reviewing product labeling, dose, and dose modification instructions. In the postmarketing period, FDA is taking a more active role in attempting to identify common use errors and in developing strategies to reduce those errors. Examples of these efforts include the publication of Safety Alerts, Public Health Advisories, guidances, brochures, and other educational information. (See Appendix F.)

Remaining uncertainties

Given current scientific and medical knowledge, it is not possible to learn everything about the effects of a medical product. For example, new information about long-marketed products (e.g., digoxin) often becomes available as a result of further scientific study or new technologies. Therefore, a degree of ***uncertainty*** always exists about both benefits and risks from medical products. Several types of uncertainties exist.

Unexpected side effects

Unexpected side effects are those that were not identified as potential risks prior to product marketing. The contribution of serious adverse events resulting from unexpected side effects to the overall rate of serious adverse events is relatively small. Working together, manufacturers, clinicians, and the FDA have created an elaborate product development and premarketing review system to identify risks prior to marketing and thus minimize the occurrence of unexpected side effects. This system enables most of these types of risks to be identified.

There are risks, however, that are difficult to identify before a

product goes on the market. Some very rare, serious or life-threatening side effects may be recognized only after marketing. These rare side effects are not usually identified during medical product development because they happen so infrequently.

As is the case with a medication or device error that results in injury or death, serious adverse events resulting from unknown side effects often gain widespread media attention because they are less acceptable to the public than injury resulting from known side effects. When these kinds of serious adverse events happen, they lead to questions about the quality of FDA's premarketing review process.

Long-term effects

Another type of uncertainty relates to the long-term outcomes of many medical interventions, including pharmaceutical or device interventions. Because long-term studies to assess these types of risks are not required prior to product approval or for continued marketing, considerable uncertainty exists about long-term side effects (particularly in the chronic disease setting). Pharmaceuticals, in particular, may provide short-term benefits, but may be associated with increased mortality or other serious long-term injuries.

Effects of off-label uses

Marketed products frequently are used to treat conditions that were not studied during clinical development (i.e., off-label uses). When products are used *off label*, there is usually greater uncertainty about both the benefits and risks because less information on safety and effectiveness is available. Unexpected adverse events may occur in this context.

Effects in populations not studied

Some groups (children, pregnant women) may not be studied before marketing. Additional uncertainties about risks (and benefits) occur with use in unstudied populations.

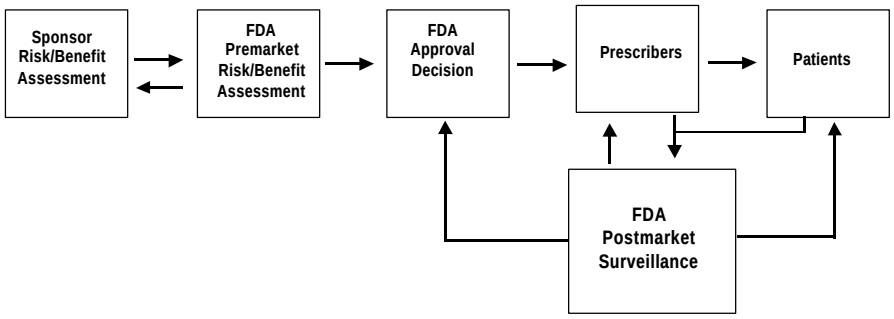
WHAT IS FDA'S ROLE IN MINIMIZING RISK?

Traditionally, FDA has filled several important roles in minimizing the risks associated with using medical products. The Agency establishes and enforces product quality standards intended to prevent defective products from reaching the market. For products

of acceptable quality, the central element of FDA's risk management is controlling product entry to the marketplace. The majority of FDA program resources are devoted to premarketing scientific risk identification and assessment and approval or nonapproval. Significant, but substantially fewer, resources are devoted to postmarketing surveillance and risk assessment activities. The Agency's role in premarketing risk identification and assessment and postmarketing surveillance and assessment are depicted in the following figure and described briefly here.

FDA Role in Medical Products Risk Management

(Rx Products)



Premarketing risk identification and assessment

FDA's premarketing review process quantifies risks detected during the clinical development of a medical product and evaluates how carefully any potential risks were assessed by the product's manufacturer. Risks related to drug-drug interactions and the potential for medication or device error are assessed. The known risks, along with any deficiencies in safety testing, are then weighed during the approval decision and described in the labeling of approved products.

Deciding whether a product's benefits outweigh its risks inevitably involves making judgments. The decision-maker must weigh a variety of complicated information and take into account a number of other considerations. The need for judgment means there can be disagreement. FDA attempts to deal with any differences of opinion by obtaining input from advisory committees and public

hearings, and by systematic, documented review procedures and decision records. Part 2 of this report discusses the scientific and procedural quality of the FDA's premarketing review process and evaluates whether it is performing as well now as it was prior to the implementation of PDUFA.

Postmarketing surveillance and risk assessment

FDA's postmarketing risk surveillance and assessment, which are described in more detail in Part 3 of the report, rely primarily on two methods of adverse event reporting to the Agency: (1) direct, voluntary reporting by health professionals and consumers and (2) mandated reporting by pharmaceutical manufacturers. Mandated reporting by manufacturers is based primarily on the voluntary submission of reports to manufacturers from user facilities, healthcare professionals, and consumers. Within the Agency, medical, statistical, and epidemiological experts use these reports to continually evaluate a product's record.

The Agency's postmarketing surveillance programs focus primarily on (1) identifying events that were not observed or recognized before approval, and (2) identifying adverse events that might be happening because a product is not being used as anticipated.

During the past decade, FDA has improved its methods for obtaining and assessing postmarketing information related to adverse events. The Agency's approaches to postmarketing risk assessment enable it to assess the likelihood and seriousness of adverse events to weigh them against the benefits of using a medical product. Once new risks have been identified and assessed, a decision about the effect on overall safety must be made and the appropriate actions taken. Actions can include requiring an update of a product's labeling information, sending out a Dear Healthcare Professional letter, or rarely, reevaluating an approval decision.

CONCLUSIONS

Public debate on the risks associated with using medical products often overlooks just how little is known about the various sources of risk and the system failures that result in patient injuries. Consequently, bad outcomes are sometimes attributed to the wrong cause, and remedies are proposed to target the wrong sources.

Under existing regulations, the Agency's work is aimed at reducing

product defects and minimizing the occurrence of adverse events. The philosophy is that if Federal controls can eliminate most of the risks associated with using medical products, a properly informed medical community will manage the remaining risks.

The next part of this report addresses the Commissioner’s questions about FDA's premarketing review and risk assessment. The Task Force discusses the rates of unexpected serious adverse events before and after implementation of PDUFA and reviews the Agency's quality control system. We also identify factors in the current development process that could be limiting the Agency's ability to identify risks during the review process.

PART 2: IS THE FDA MAINTAINING THE QUALITY OF ITS PREMARKETING REVIEWS?

Commissioner Jane Henney, as one of her first initiatives, created this Task Force to investigate concerns being expressed by critics and to look into the Agency's role in managing risk. She asked the Task Force to determine if the Agency was maintaining adequate quality control (QC) over its premarketing review decisions. To address this, the Task Force focused this part of its evaluation on the following:

- Has there been an increase in the rate of unanticipated serious adverse events from medical products that have gone on the market subsequent to PDUFA?
- How well is the Agency's QC system for premarketing review and marketing decisions functioning?
- Are there any factors that could be affecting the Agency's ability to detect potential risks during its premarketing review?

HAS THE RATE OF SERIOUS ADVERSE EVENTS INCREASED?

Methodology

To answer this question, we first looked at a 1990 report by the U.S. General Accounting Office (GAO) on adverse events first

reported after a medical product goes on the market.[1] GAO's 1990 report evaluated serious adverse events discovered during the postmarketing period for drugs approved between 1976 and 1985. The report defined previously unanticipated serious adverse events as events resulting in (1) the withdrawal of a product, (2) the addition of label warnings, (3) the making of a significant label change, and (4) issuing a Dear Healthcare Professional letter.[2]

Applying the same methods used in the GAO report, we examined the rate of previously unanticipated serious adverse events occurring after approval under the faster PDUFA-era reviews. We then compared the GAO's pre-PDUFA datasets to our own post-PDUFA datasets. To evaluate only those drugs where the review was primarily conducted under PDUFA, products approved in 1992 or 1993 were not included. And, to allow the effects of a product's postapproval market rollout to be considered, products approved in 1998 or 1999 were not included. (See Appendix A.)

Findings

The rate of withdrawals has decreased

The results of our comparison of the data showed that there has been no increase in the rate of ***drug withdrawals*** in the United States since PDUFA was enacted.[3] As the graph at the end of this section shows, the Nation has experienced a 1- to 3.5-percent rate of postmarketing withdrawals for new products during the last several decades.[4] In most cases, withdrawals occur during the first or second year following approval. But there have been cases where drugs were withdrawn 3, 4, and up to 5 years after approval. Of the five drugs withdrawn for safety reasons after 1992, two

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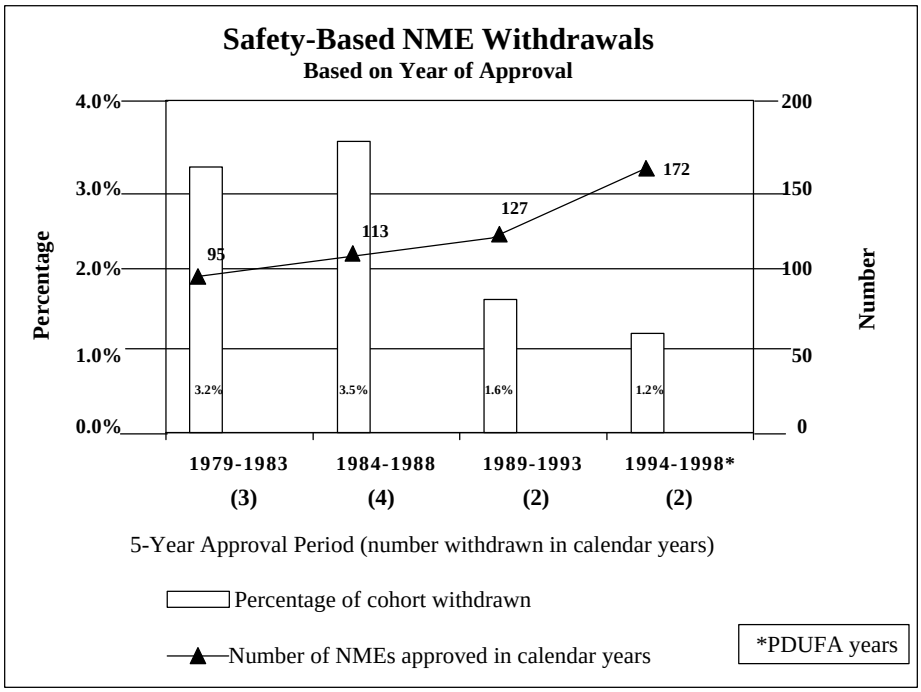
[1] Government Accounting Office, *FDA Drug Review — Postapproval Risks 1976 - 1985*, GAO/PEMD-90-15, April 1990.

[2] A *Dear Healthcare Professional letter* is usually sent by the manufacturer to inform healthcare professionals about important safety-related changes to product labeling.

[3] A review of the rate of unanticipated adverse events leading to drug withdrawals is reported in detail in Friedman, M.A., J. Woodcock, M. Lumpkin, J. Shuren et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?" *JAMA*, Vol. 281, No. 18, May 12, 1999.

[4] FDA, Center for Drug Evaluation and Research, *1998 Report to the Nation*, May 1999.

were approved before PDUFA was implemented.[5] As a result, some additional drugs approved under PDUFA could be withdrawn in the future. Nonetheless, because the rate of withdrawals since 1992 shows a downward trend, even if a proportionate number of late-appearing problems were to result in withdrawals, an increase in the overall rate as compared to the pre-PDUFA era will most likely not occur.



The rate of serious adverse events has decreased

The Task Force has found that available evidence does not support the charge that ***unanticipated serious adverse events*** are occurring at a higher rate since the implementation of PDUFA. We found that under PDUFA, there has been a lower rate of serious adverse events identified during the postapproval phase (30.3 percent of products) than during the 1976 to 1985 baseline years (51.5 percent

[5] Redux, Pondimin, Seldane, Duract, and Posicor were withdrawn from the market in 1997 and 1998; Seldane and Pondimin were approved prior to PDUFA.

of products). The table, below, shows the new molecular entities with significant postapproval label changes resulting from reports of serious adverse events, 1976 to 1985 compared to 1994 to 1997.

Table – New Molecular Entities with Significant Postapproval Label Changes, 1976 to 1985 compared to 1994 to 1997

Period	*Labeling Changes Associated with Significant Postapproval Risk*		*Total*	*Percent with Significant Label Changes*
	No	*Yes*		
1976 - 1985	*96*	*102*	*198*	*51.5%*
1994 - 1997	*99*	*43*	*142*	*30.3%*

Among drugs approved following implementation of PDUFA, the highest annual rate of postmarketing serious adverse events was still well below that in GAO's baseline data. As in the GAO audit, our comparison was limited to new drugs. New biological therapeutic and vaccine products had five significant postapproval events for 29 products approved from 1994 through 1997 (17 percent); new medical devices subject to premarketing approval were not evaluated.

Although the 30-percent proportion is better than that previously found, it still raises the question of why these serious risks are not discovered before marketing. There are several reasons for this. For example, some kinds of serious side effects, such as those resulting from drug overdoses, cannot be studied ethically in humans and can only be learned about from overdoses of drugs that are on the market. In addition, in some cases, the Agency approves drugs intended to treat serious and life-threatening diseases with less information than usual, knowing that more will be learned during the postmarketing period.[6] Finally, as discussed later in this Part, it is impossible to detect or predict before medical product approval every possible drug interaction, unusual clinical situation, or rare side effect that could lead to harm once a product is on the market. Nevertheless, the Agency's goal is to minimize the number

[6] Patients with serious and life-threatening diseases who lack effective treatment have told the Agency that prompt access to new treatments is extremely important to them. These patients are willing to accept greater uncertainty about risks and benefits in exchange for earlier access.

of serious adverse events that occur after a medical product is approved.

HOW WELL IS THE AGENCY'S QUALITY CONTROL SYSTEM WORKING?

Although the process differs to some degree from Center to Center and from product type to product type, the FDA approval process usually involves a complex, and thorough investigation of the data submitted in a medical product application. In the review of pharmaceuticals, for example, the goal of this investigation is to determine (1) if the results of well-controlled studies provide substantial evidence of effectiveness and (2) if the results show the product is safe under the conditions of use in the proposed labeling (i.e., the benefits of the product outweigh the risks).

Under current law, all new drugs must be shown to be effective, as well as safe, before they can be approved for marketing. After a manufacturer (or sponsor) has completed certain preliminary testing of the new product in animals (preclinical testing), it can seek approval from the FDA to begin limited testing of the product in humans. FDA estimates that on average it takes 8.5 years to study and test a new drug before the Agency can approve it for the general public, including early laboratory and animal testing, as well as later clinical trials using humans.

FDA's review of the application, including site inspections and other interactions with the product's sponsor, takes approximately 12 months.

When the application is received, it is assigned to a review team based on the type of drug and intended use. The typical review team (see the box below) for a new drug evaluates test results submitted in the application. The documentation required in an application is supposed to tell the drug's whole story, including what happened during the clinical tests; how the drug is constituted; the results of animal studies; how the drug behaves in the body; how it is manufactured, processed, and packaged; and any other available material. FDA also requires samples of the drug and its proposed labeling (prescribing information or package insert). Using the submitted data, the FDA review team decides whether the studies submitted by the product's sponsor show it to be safe and effective for its intended use. The purpose is to determine whether the drug is safe enough to be marketed and what its labeling should say about directions for use, side effects, and warnings.

Typical Agency Drug Review Team

Chemists focus on how the drug is made and whether the manufacturing process and packaging are adequate to ensure the identity, strength, quality, and purity of the product.

Pharmacologists and toxicologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.

Physicians evaluate the results of the clinical tests, including the drug's adverse as well as therapeutic effects, and whether the proposed labeling accurately reflects the effects of the drug.

Clinical pharmacologists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated.

Statisticians evaluate the designs for each controlled study and the analyses and conclusions for safety and effectiveness based on the study data.

Microbiologists also participate in the review of anti-infective drug products and of products that occur as solutions or as injectables.

In the case of medical devices, teams of review scientists include engineers, biological scientists, materials experts, and clinicians. These experts review the valid scientific evidence submitted by sponsors to determine the safety and effectiveness of devices either by comparison to a previously marketed (predicate) device or through a premarket approval application (PMA) that establishes reasonable assurance of safety and effectiveness.

After FDA primary reviewers finish their evaluation, additional review is provided by supervisory personnel. Regulations require that the decision process be appropriately documented in an administrative record.[7] And an employee or someone outside the Agency can request an internal Agency review of a decision.[8]

One key part of FDA's mission is to ensure that manufacturers identify potential risks during drug development and advise prescribers about them in product labeling. Failure to identify and advise the healthcare community about even comparatively rare

[7] 21 Code of Federal Regulations 10.70.
[8] 21 Code of Federal Regulations 10.75.

risks is unacceptable if their identification could reasonably have been expected. This is not to say a perfect understanding of a drug's safety can be attained during drug development. In the end, approval decisions are based on the ***judgments of Agency experts***, resulting from their review of data collected during clinical trials.

The data from trials are always limited by the size of the trial. But, if the trials are well-designed, the data should be adequate to permit reasonable judgments concerning a product's safety. For this reason, FDA focuses considerable attention on the quality control of its premarketing program. The Task Force undertook an audit of the current quality control system to see how well it was functioning.

Methodology

To measure the adequacy of the Agency's quality control system, the Task Force compared it to the International Standards Organization (ISO) quality framework. ISO 9001 is a generic, worldwide quality management system standard promulgated by the International Organization for Standardization (ISO). ISO is currently completing a revised edition of this standard, ISO 9001:2000.

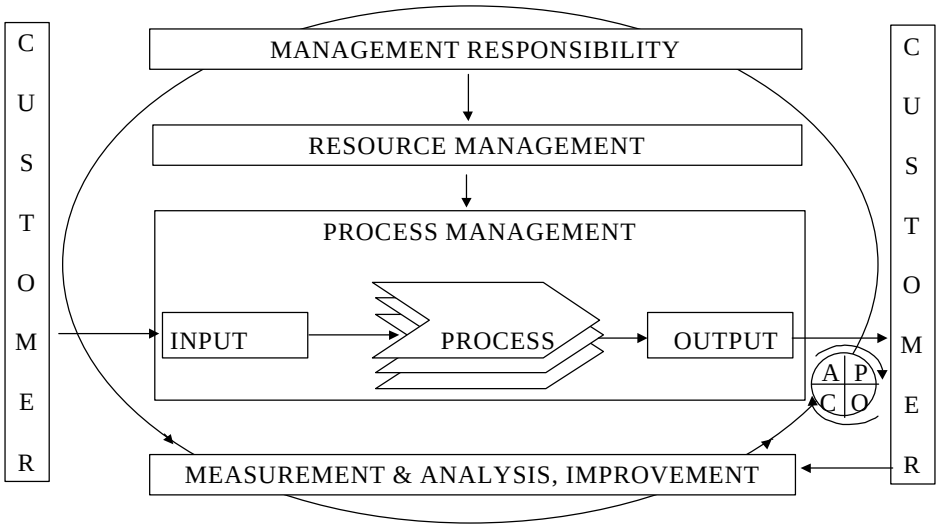
ISO 9001:2000 sets forth the quality management system requirements an organization should have in place to demonstrate its capability to meet customer (stakeholder) needs. The process-based structure envisioned by ISO 9001:2000 is built around four key areas of concern:

- Management responsibility (policy, objectives, planning, quality management system, management review);
- Resource management (human resources, information, facilities);
- Process management (customer satisfaction, design, purchasing, production); and
- Measurement, analysis, and improvement (audit, process control, continual improvement).

The ISO framework (see figure below) does not impose a uniform quality management system, but instead provides criteria an

organization can use. FDA has wide-ranging public health responsibilities, and its premarketing review process seeks to meet the needs of the public, industry, and healthcare professionals. The creation and application of a comprehensive quality control system helps ensure FDA's premarketing review process meets its public health responsibilities.

International Standards Organization Quality Framework



FDA mapped its premarketing review quality control functions according to the elements of the ISO 9001:2000 framework to ensure that FDA's system contains the necessary elements. Each of the three Centers prepared a detailed inventory of those procedures and processes that meet the specific elements in the ISO system. (See the general listing of relevant ISO elements in Appendix A.)

Because of the diverse products, legal requirements, and organizational structures that were to be audited, the audit focused on the existence and application of control systems. In every Center, an extensive clearance process is relied on as part of the control system.

In addition, samples of recent product approval records from FDA's Center for Drugs, Center for Biologics, and Center for Devices were reviewed for their conformance to the existing quality

control standard operating procedures.

Findings

The Task Force audit found that there is substantial conformance in FDA's quality control system to the principles of quality assurance (QA) and quality control (QC) as described in ISO 9001:2000. The FDA applies management responsibility, resource management, process management, measurement analysis and improvement, and documentation of control activities to its premarketing review and risk assessment process.

Reviews continue to be subject to 100 percent quality control

Premarketing reviews continue to be subject to 100-percent quality control. At least one level (and regularly, three levels) of expert subject-matter supervisors must concur with, or make documented revisions to, every primary review.

Several QC areas need enhancing

By undertaking this review of FDA's quality control system, the Task Force was able to fulfill one of the elements previously missing from its quality control system: a comprehensive executive management quality review of the Agency's premarketing review program. The Task Force found that, in several quality control areas, the Agency has begun development of processes to satisfy a particular ISO QA/QC element, but has not yet fully implemented them.

One of the most obvious underdeveloped areas was in establishing, administering, and documenting explicit training requirements for review staff. The Agency has relied on professional training, employment qualifications, supervisory mentoring, and annual performance reviews to ensure that the review staff possess the knowledge, skills, and abilities to perform their assigned duties. Additional professional development, attendance at internal and external professional educational meetings, in-house core competency training, and in-house Staff College training have been offered by all three Centers. But continuing education has not been systematically required of all review staff as a means of ensuring eheir continued qualifications to perform their assigned work.

A second area that FDA needs to focus efforts on is compiling explicit, detailed standards against which FDA reviewers are to evaluate new medical products. The goal of the ongoing Good

Review Practice project is to systematize existing knowledge of what to look for when conducting a review. The project will document in a reviewer guidance the parts of an application that are most important to evaluate and what to expect when evaluating them. Documenting review expectations at this level is unusual, as it involves analyzing complex, knowledge-based activities. But once the guidance is completed, the Agency can be more confident that consistent and high-quality reviews are being performed.

During the audit of FDA's quality control system, the Task Force paid particular attention to whether differences of scientific opinion among primary reviewers and supervisors are being addressed within a quality control framework. In addition to the regulations mentioned above requiring the documentation of decisions and supervisory review of decisions upon request of an employee or person outside of the Agency, all FDA offices have written procedures on the specific processes for making and documenting scientific review opinions.[9] These procedures delegate responsibility for final decisions to individuals with extensive regulatory experience who are supported by multidisciplinary scientific teams. The procedures contain explicit steps for resolving differences in scientific opinion among the reviewers and require the official responsible for the decision to document the reasons for rejecting dissenting recommendations.

The QC system is regularly followed

The Task Force found that, overall, although some elements of FDA's quality control system could more closely comply with the proposed ISO framework, the key elements of the ISO QA/QC system are in place and are regularly followed. We believe that FDA's premarketing review and decision processes are being managed to produce high-quality decisions on new medical product applications. However, in the course of the audit, the Task Force identified factors in the current medical product development process that could be affecting the Agency's ability to minimize unknown risks.

[9] See, for example, CDER's *Manual of Policies & Procedures* 4151.1 on "Resolution of Disputes: Roles of Reviewers, Supervisors, and Management: Documenting Views and Findings and Resolving Differences."

WHAT FACTORS IN THE DEVELOPMENT PROCESS COULD AFFECT RISK IDENTIFICATION?

The clinical community and FDA have long recognized that, even given the flawless functioning of both the manufacturer's product development process and the FDA's review process, factors inherent in the current medical product development system will continue to limit FDA's ability to identify all potential risks in new medical products. In interviews with the directors of the Center for Drugs, Center for Biologics, and Center for Devices and with the premarketing biostatistics office directors about their experience with premarketing reviews and about the product development process and its limitations, we identified the following factors that could be affecting the Agency's ability to identify potential risks prior to medical product marketing.

Trials expose only a relatively small number of people to a product

The number of patients exposed to a product increases 1,000-fold or more when the new product moves from the clinical trial setting to the real world setting. For example, clinical trials for most pharmaceuticals enroll and follow between 1,000 and 10,000 patients. For products intended to treat chronic, non-life-threatening conditions that occur in large populations, the International Conference for Harmonisation (ICH) [10] recommends a baseline safety database that typically involves at least 1,500 patients, usually achieved over multiple trials. The patient sample size and 6-month exposure time recommended by ICH are designed to reliably (95 percent of the time) identify events happening at the 1-percent level and are not expected to identify more rare events. Yet, in the first year of marketing, a successful new medical product can easily reach millions of Americans. This means that for an adverse event that occurs only once in 1,500 patients (considered rare), the chance of seeing such an adverse event goes from a 50-50 chance of seeing one in a clinical trial to seeing as many as 1,000 adverse events in the first year the product is on the market. In addition, preapproval trials rarely gather long-term experience with a product (more than 6 months) because often no more than a few hundred individuals use the product for 6 months

[10] The FDA is one of the six founding members of the International Conference on Harmonisation (ICH), which is a joint initiative involving both regulators and industry in scientific and technical discussions of the testing procedures that are required to ensure and assess the safety, quality, and efficacy of medicines.

or longer.

As a result, information on risks that occur only rarely may be entirely absent from the premarketing database, or may be represented by, at most, only a very few cases. If a risk is novel and not an expression of common patterns of toxicity, there may be insufficient evidence to identify the product as the cause of the event. In addition, adverse events that occur at a background rate in the treated population may be difficult to detect.[11] When considering long-term exposure to a medical product, there is little expectation that adverse events that don't occur until 2, 3, or more years of use will be identifiable based on the premarketing data. This is true even for medical products that will be used for a lifetime.

Despite these drawbacks, the size and duration of clinical trials were not determined by chance. Protocol designs for trials reflect decades-long experience studying failures to detect adverse biological effects, identifying statistical design issues, analyzing what can reasonably be achieved during clinical investigations, and carefully considering the practical ability of manufacturers and clinical investigators to regularly conduct large-scale trials. Clinical trial investigators expect the majority of severe toxicities to be detected through a combination of high-exposure animal studies and the current profile of trial size and duration. Under the current clinical trial design, the common modes of major toxicity ─ bone marrow suppression, hepatocellular damage, renal damage, neuropathy, and alteration of CNS function ─ are regularly detected and, except for economic decisions, account for the majority of medical products not progressing from clinical trial to the marketplace. Novel risks are harder for the clinical development system to find, yet once identified, they are also evaluated in trials. For example, because practolol (a beta-blocker whose IND application was discontinued in 1977) caused cataracts, clinical trials for pharmaceuticals now require that some patients be monitored for cataracts.

Clinical trial patients aren't real world patients

During the development of a new medical product, clinical trial designers want to demonstrate effectiveness clearly. They want to find the greatest achievable therapeutic effect consistent with safe

[11] The *background rate* of an event in a given population is the rate at which events occur in people who are not exposed to the given product.

use. To accomplish this, they seek a homogeneous study population with the goal of preventing statistical *noise* from obscuring the treatment effect. To achieve homogeneity, clinical trials often systematically exclude special populations — patients with concurrent diseases, with concurrent drug use, or at age extremes, or who otherwise are felt to be at risk of noncompliance. Trials also often exclude people with any other factors that may make it more difficult to measure effectiveness. Yet, the people being excluded may be precisely the people who ultimately will be using a product and in whom toxicities are most likely to occur.

Clinicians and FDA regulators have long recognized this exclusion problem in designing clinical trials. During the last two decades, the Agency has moved to ensure the inclusion of reasonable numbers of both genders, individuals with the ethnic profile of the population that will be using the product (the target population), and individuals at the extremes of age. More important, the Agency has encouraged the design of large simple trials that more accurately reflect normal, real world use patterns. Unfortunately, large simple trials remain uncommon in human medical product development. Clinical trial populations still do not completely reflect the population who will be using a product once it goes on the market.

Clinical trial patients are carefully screened

Another disparity exists between patients in the clinical trial setting and the real world setting because clinical trial screening practices ensure that essentially all patients have the condition being investigated. Once a product goes on the market, less stringent diagnostic criteria are applied than were applied during trial screening. In addition, some patients will be given a product that was intended to treat a different disease (poor product choice). Off-label drug use also may rapidly proliferate. In the case of both poor product choice and off-label use, patients may differ greatly from the trial population; they may be receiving different doses for different lengths of time; and they may be facing very different risks.

The extent to which patients in clinical trials differ from patients in the general population compounds the problem created by the disparity between the size of the clinical trials and the vastly larger population to whom a medical product is marketed. Not only are 1,000 times as many people exposed to a product in the real world,

but many of them will differ significantly from the clinical trial patients for whom safety data have been collected.

Clinical trial patients are closely monitored

Another way the clinical trial setting differs from the real world setting is that, in addition to effectiveness, clinical investigators are studying safety. They are on the lookout for toxicity and promptly cease using a product if a toxic event occurs. Clinical trial patients are seen by their clinician for reevaluation at regular intervals; they are advised how to self-monitor for symptoms that may reflect toxicity and to seek prompt medical attention if symptoms occur. Finally, they receive regular laboratory tests for early evidence of target organ toxicity.

Most healthcare practitioners follow the recommendations for monitoring in the Precautions and Warnings sections of the labeling. But even highlighted, explicit warnings sometimes go unheeded. One result of the shift from the clinical trial setting to the real world setting is that toxic effects are less likely to be detected early, when they are most reversible. For example, assume a given product produced *biochemical evidence* of hepatocellular injury in 3 percent of trial patients, but caused no *observed* cases of overt hepatitis in the clinical trials (i.e., there were fewer than the 0.3-percent incidence of overt hepatitis that the clinical trials were designed to detect). Transferred to the real world setting, the same 3-percent hepatocellular injury rate could well produce a 1-percent incidence of overt hepatitis and occasional (0.5 percent) liver failure. The higher incidence and more severe consequence would result because the liver damage was not detected early and drug use was not stopped before producing irreversible damage. In cases where not a single incidence of significant liver damage occurred in the clinical trial setting, undetected hepatitis, liver failure, and death (at a one-in-5,000 patient rate) could easily produce dozens of deaths during the first year that a product is on the market.

Market rollout affects risk identification

Once products enter the market, one might think that use patterns would minimize the occurrence of such events, and any adverse event would be detected quickly and its impact mitigated. Yet, experience has shown that, once approved, new products reach consumers so quickly in the U.S. market that often dozens to hundreds of adverse events can occur before they are recognized and action is taken to reduce their effects. (FDA's programs to

detect such events are addressed in more detail in Part 3 of this report.) Some of the effects of market rollout are discussed in the following paragraphs.

Market rollout often targets a broad population

Market rollout often targets a broad population that does not resemble the population in which the product was tested and for which the product was intended. Use patterns show that a product is often quickly and widely positioned in the marketplace even if time-tested alternatives to the new product are available. The potential consequences of this practice are clear when one retrospectively looks at products for which unknown risks and serious adverse events led to market withdrawals (e.g., Omniflox [temafloxacin], Duract [bromfenac]). In most of these cases, a patient who suffered a major adverse event could have been prescribed any one of a number of alternative products with established safety records.[12]

Sometimes, a new medical product has offered treatment for patients where essentially nothing else was available (e.g., AZT), or where existing alternatives are very unsatisfactory (e.g., erythropoietin). When a medical product is developed that demonstrates a clear therapeutic benefit, FDA recognizes its importance by expediting the review. However, most new products are incremental or niche improvements over alternatives that are already on the market. For example, the improvement may be having a better treatment effect (i.e., an incremental improvement), or it may even be limited to dosing convenience (i.e., a niche improvement). Many medical products lack even this often modest demonstration of clear benefits since they are molecular mimics developed and marketed based on evidence showing only that they are effective compared with a placebo.

In these cases, earlier-approved products to treat the same indication, having stood the test of time, will be less likely to produce previously unrecognized toxic effects. When time-tested alternatives to a new medical product are available, it may be prudent to consider how quickly to expose which patients to the new medical product, especially if it has exhibited serious risks during development.

[12] In cases where no alternative exists, a product would not be withdrawn, but relabeled to achieve more careful use.

Economic and organizational factors drive market rollout strategies

To better understand the general approach to medical product development and rollout strategies, it is useful to consider some of the economic and organizational factors that influence decisions made by pharmaceutical manufacturers.

The development and testing of a new medical product can be difficult and prolonged and typically require an enormous front-end financial investment. If manufacturers are to survive, thrive, and make profits, they must recover the front-end costs of product development and testing. Included among these costs are the losses associated with products that are abandoned during development. When similar products are under development by different manufacturers, a manufacturer is particularly driven to achieve rapid, widespread market penetration and prescriber loyalty. Consequently, firms tend to rollout new products rapidly and market them aggressively.

Manufacturers usually recognize that their long-term goal is to ensure high-quality products while minimizing the frequency of serious adverse events. Yet, they may not always recognize when the incentives they offer — salary increases, bonuses, or stock options tied to milestones or to the sales volume of a new product — conflict with this goal. Once a new product is approved by FDA, the responsibility for launch and marketing usually falls on entirely different personnel than were involved in developing the medical product. Marketing personnel may not always completely recognize how their product placement and positioning decisions affect the use of a product and the risks that accompany that use.

Although FDA has little direct influence over a manufacturer's product marketing choices, the Agency should consider potential marketing approaches when designing and implementing its QA/QC system.

The FD&C Act standards also affect market rollout strategies

The reality is that a rapid rollout strategy usually results in a new medical product moving quickly from testing in a few thousand clinical trial patients to, perhaps, millions of new prescriptions. This leap in numbers takes place just months after launch, before there is time for feedback through postmarketing reporting. Although driven to a great extent by economic issues, this pattern is also, in part, a consequence of the way the Federal Food, Drug, and

Cosmetic Act (FD&C Act) establishes standards for medical product approval.

The FD&C Act standards for safety and effectiveness permit approval based on an independent demonstration of safety and effectiveness for each product. Pharmaceutical manufacturers have strongly objected to the use of review criteria or practices that they believe might lead to a comparative effectiveness standard. Yet, if use of a new product were evaluated comparatively, the potential extent of injury from an unknown risk might be reduced because the product's initial postmarketing use could be limited to those patients who have been shown to experience a clear therapeutic benefit over an alternative product. In such a case, a smaller segment of the population would be exposed to any unknown risks during the early postmarketing phase. The merits and liabilities of changes (both more and less stringent) to FDA's approval standards have been the subject of an ongoing public policy debate. Any impact on product safety is but one aspect of that debate.

CONCLUSIONS AND RECOMMENDATIONS

The Task Force found that the data show no increase in the rate of drug withdrawals since PDUFA. There is also no evidence that drugs reviewed under PDUFA (the 1994-1997 cohort) have resulted in higher rates of serious adverse events identified postmarketing than have drugs reviewed before PDUFA. In fact, we found the rates of serious adverse events identified postmarketing were lower for drugs reviewed under PDUFA.

The Task Force also found that, overall, the key elements of FDA's quality control system are in place and are regularly followed. FDA's premarketing review and decision process are being managed to produce high-quality review decisions.

Despite these findings, the Task Force believes that the three Centers that conduct premarketing review of human medical products could enhance the application of FDA's quality control system in the following ways:

Recommendations

1. Initiate steps to have each Center establish separate QA/QC units to support the QA/QC system as a normal part of all activities. Responsibilities should include the following:

- Peer review a sample of product approval review administrative records for quality of the analysis and completeness of the documentation.

- Establish procedures for continuation of review when there has been an administrative disruption of the process (e.g., loss of primary reviewer, change of division).

- Prospectively track scientific disputes among reviewers and evaluate whether the disputed issue is predictive of problems after marketing.

2. Ensure and document ongoing professional education and current core competency training for all reviewers.

3. Complete the Good Review Practice (GRP) documents and keep them current.

4. Systematically analyze significant postmarketing events and incorporate them into GRP as lessons learned.

Additional options

Options that could address, in part, the factors in medical product development that limit the identification of some risks include:

1. Evaluate the practicality and value of expanding the use of large, community-based simple trials designed to identify serious adverse events in a larger and more representative patient population prior to approving the product for widespread use.

2. Develop tools to concentrate early postapproval use in populations for whom an advantage of the new product over alternative products has been demonstrated.

PART 3: HOW DOES FDA CONDUCT POSTMARKETING SURVEILLANCE AND RISK ASSESSMENT?

It is simply not possible to identify all the side effects of drugs before they are marketed.

Wood, Stein, and Woosley, *New England Journal of Medicine*, 339, pp. 1851-1854 (1998)

The second area the Task Force was asked to evaluate is FDA's postmarketing surveillance and risk assessment and its strengths and weaknesses. A vital part of FDA's mission is to ensure that medical products currently available in the United States are safe and effective. The Agency monitors marketed human medical products for unexpected adverse events. FDA surveillance programs alert the Agency to potential threats to the public health and help Agency experts identify the need for preventive actions, such as changes in product labeling information and, rarely, reevaluation of an approval decision.

The Task Force believes that FDA's postmarketing surveillance and risk assessment programs are, for the most part, accomplishing the purposes for which they were designed. However, recent regulatory changes, an increasingly complex healthcare environment, and the emerging global marketplace present challenges to existing systems. For these reasons, FDA has been reassessing its surveillance approaches to ensure their continued effectiveness in monitoring the safety of marketed human medical

products.

This Part of the report describes the Agency's ongoing postmarketing surveillance and risk assessment programs. We outline briefly efforts that are underway to enhance these programs. Finally, we identify some options for further enhancing the Agency's postmarketing program.

OVERALL POSTMARKETING RISK ASSESSMENT IS COMPLEX

Under the current system, FDA shares responsibility for postmarketing risk assessment with manufacturers, healthcare providers, user facilities, and patients. Each participant has a role in monitoring and evaluating adverse events associated with medical products, as well as taking appropriate corrective action. The roles assigned to manufacturers and the FDA are defined primarily by statute, while the roles of other stakeholders are more flexible in most cases.

The specific objectives of FDA's postmarketing risk assessment programs are to detect adverse events not previously observed, improve understanding of the potential severity of previously anticipated risks, detect events resulting from drug interactions or drug effects in particular populations, and assess the potential for causal relationships.

Manufacturers of prescription medical products are required to submit adverse event reports to the FDA. In addition, drug and biological product manufacturers must submit either error and accident reports or drug quality reports when deviations from current good manufacturing practice (CGMP) regulations occur. For medical devices, manufacturers must report to the Agency the voluntary recall of any products that are in violation of the Act and that pose a risk to health.

FDA is responsible for inspecting the manufacturing facilities to determine if they comply with the regulations, including the regulations that require reports to the Agency. The Agency may issue warning letters and take other regulatory actions when a manufacturer fails to comply with the reporting requirements.[1]

[1] Appendix B contains some examples of regulations, guidance, proposed rules, and International Conference on Harmonisation (ICH) documents on postmarketing surveillance.

For a number of reasons, changes are occurring that will affect the Agency's current postmarketing system. First, PDUFA and the Modernization Act of 1997 have resulted in some changes in postmarketing reporting requirements. For example, with regard to medical devices, the Modernization Act directs the FDA to move away from universal, mandatory adverse event reporting by user facilities to a system based on reporting by a representative sample of facilities.[2] The Modernization Act also provides for sponsors of a drug that have entered into an agreement with the Agency to conduct a postmarketing study to report annually to the Agency on the progress of the study or the reasons for the failure of the sponsor to conduct the study.[3]

In addition, shifts in the healthcare environment and in international marketplaces are affecting the potential for adverse events caused by medical interventions. For example, with patients now being treated by multiple healthcare providers, a single provider may not have full knowledge of the patient's medical history and use of various medicines. Prescribers' lack of information can lead to increased risk of drug interactions, as one physician may not be aware of what another has prescribed. The increasingly global marketplace for medical products also could result in a greater potential for rapid, large-scale patient exposure to new products and carries a proportional potential for more unexpected adverse events. Finally, the rapid development of new medical interventions for a variety of previously untreatable (or less satisfactorily treatable) conditions results in more individuals using medical products. The availability of a new class of antidepressants leading to a substantial increase in the number of individuals receiving drug treatment for depression is just one example. These shifts in the healthcare environment are challenging the existing risk management system and should be considered in each participant's approach to postmarketing risk assessment.

One concern raised by the healthcare community is whether the Agency can rapidly collect and analyze the vast amount of postmarketing risk assessment information and respond in a timely manner to findings of postmarketing surveillance.

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[2] Section 519(b)(5) of the FD&C Act (section 213 of the Modernization Act).

[3] Section 506B of the FD&C Act (section 130 of the Modernization Act).

FDA USES A NUMBER OF APPROACHES TO ASSESS RISK

FDA uses a number of postmarketing risk assessment approaches to ensure the continued safe use of medical products. These include spontaneous reporting systems to rapidly identify potential new problems; large healthcare databases with product use linked to subsequent diagnoses, hospitalizations, and other adverse events; cohort and case-control studies conducted as needed to investigate a specific safety issue in depth; and registries initiated when potential risks (particularly those apparent only with long-term follow-up) are sufficient to warrant identification and active follow-up of individuals exposed to a product. FDA relies on multiple approaches because no single approach is sufficiently comprehensive to permit full evaluation of all important problems. The various approaches the Agency is using for postmarketing surveillance are described briefly in the following pages. The program descriptions are grouped according to the type of product being monitored and the Center doing the monitoring.

Spontaneous reporting systems — for drugs and therapeutic biological products

FDA receives spontaneous reports of ***suspected*** adverse events from manufacturers (required by law and regulation to report to FDA), from user facilities, and from healthcare professionals or consumers. Through a program called MEDWATCH, the FDA Medical Products Reporting Program, healthcare professionals and consumers are encouraged to report serious adverse events and product problems to the FDA, the manufacturer, or both. MEDWATCH has established four methods for the public to report to FDA: phone (via a toll-free number), fax, direct mail (using a postage-paid form), and Internet (via the interactive form on the MEDWATCH website). All MEDWATCH reports are expeditiously transferred to the appropriate Center for evaluation and entry into one of the following database systems.

Adverse Event Reporting System (AERS)

FDA's current adverse event database for drugs and therapeutic biological products, the Adverse Event Reporting System (AERS), contains approximately 2 million reports. In FY 1998, more than 230,000 reports of suspected adverse events were received by AERS.

The FDA evaluates spontaneous reporting data from AERS to

identify any serious, rare, or unexpected adverse events or an increased incidence of events. When a signal of a potential adverse reaction is detected, safety evaluators consult with product reviewers, medical officers, and epidemiologists to review available data and consider further options. Focused studies may be undertaken using various epidemiological and analytical databases and other resources. Based on the results of these studies and evaluations, FDA may decide to disseminate risk information, such as Dear Healthcare Professional letters, and may initiate regulatory action.

The Agency recognizes that surveillance should focus particularly on medical products in the immediate postmarketing period and is refining its programs to ensure that these products receive special attention.

CBER Error and Accidents Reporting System (CEARS)

Errors and accidents in the manufacture of biological products are required to be reported to FDA by the product manufacturer. An error or accident is a deviation from good manufacturing practice regulations (CGMPs), applicable standards, or established specifications, or an unexpected, unforeseen event that may affect the safety, purity, or potency of a biological product, or otherwise cause the product to be in violation of the FD&C Act or the Public Health Service Act. Among other examples, reportable errors and accidents may relate to labeling, storage and distribution, or testing of a biological product.

FDA receives approximately 13,000 reports per year from biological product manufacturers. In the past 2 years, there has been a significant increase in reports submitted by the non-blood industry, including the manufacturers of vaccines, therapeutics, in vitro diagnostics, and plasma derivatives. FDA reviews and evaluates reports of errors and accidents to determine if a recall is needed. Approximately 13 percent of the reports received in fiscal year 1998 were forwarded to the appropriate district office for follow-up and evaluation as potential recall situations. Error and accident reports are coded based on the type of error or accident and entered into a database. Quarterly and annual summary reports are prepared from this data. District offices can access the error and accident database through the CBER CEARS to aid in preparation for inspections.

Drug Quality Reporting System (DQRS)

The Drug Quality Reporting System (DQRS) receives reports of deviations from CGMPs that occur during the manufacturing, shipping, or storage of prescription or over-the-counter drug products. Despite FDA's surveillance activities and enforcement of CGMPs, some drug quality defects will occur and may occasionally pose a threat. Drug quality concerns include a number of hazards, which may be due to improper formulation, packaging, or labeling.

Information reported to the DQRS is currently entered by a contractor and retrieved using an on-line system. The system is being evaluated for possible integration with AERS. In fiscal year 1998, some 2,500 reports were received resulting in the initiation of 11 recalls. Most of the recalls were due to labeling violations.

Medication Error Reports

FDA receives medication error reports on marketed human drugs (including prescription drugs, generic drugs, and over-the-counter drugs) and non-vaccine biological products and devices. Medication errors can occur when prescribing, repacking, dispensing, or administering a product. Common causes of medication errors include poor communication, patient misunderstanding, and ambiguities in product names or directions for use.

In 1992, the FDA began monitoring medication error reports that are forwarded to FDA from the United States Pharmacopeia (USP) and the Institute for Safe Medication Practices (ISMP). The Agency also reviews MEDWATCH reports for possible medication errors. Currently, medication errors are reported to the FDA as manufacturer reports (adverse events resulting in serious injury and for which a medication error may be a component), direct contact reports (MEDWATCH), or reports from USP, or ISMP.

FDA maintains a central database within the DQRS and AERS for all reports involving a medication error or potential medication error. The database contains some 7,000 reports. Unlike reports of adverse events, which always involve patient injury, medication error reports can be reported as errors with no patient injury, errors with patient injury, and potential errors (e.g., the report of a confusing product name).

FDA reviews and acts on medication errors that relate to product labeling and/or packaging. The Agency puts substantial effort into reviewing case reports to identify serious or potentially serious

outcomes that might be avoided by modifying the labeling or packaging. Each report is analyzed to determine causality. Categorizing medication errors helps the Agency perform trend analyses and make recommendations to the reviewing divisions for potential regulatory action. (See examples in Appendix G.)

Spontaneous reporting systems — for blood and blood components

The blood bank and source plasma industry submits the majority of error and accident reports received by the Center for Biologics. Most of these reports relate to donor suitability. A proposed rule that published in 1997 would expand the reporting requirement for licensed facilities to include unlicensed blood establishments and transfusion services.[4]

When a blood transfusion (or blood collection) complication is confirmed to be fatal, it must be reported to FDA within 7 days. This information is used for risk assessment and communication of risk to blood establishments, transfusion services, and physicians. Note that adverse events associated with therapeutic plasma-derivative products (such as hemoglobin) are reported in the same way as adverse events associated with drugs and other therapeutic biological products.

Spontaneous reporting systems — for vaccines

Vaccine Adverse Event Reporting System (VAERS)

Postmarketing surveillance for vaccines is handled by the Vaccine Adverse Event Reporting System (VAERS), a system independent of other FDA spontaneous reporting systems. Established in 1990, VAERS is jointly managed by FDA (the Center for Biologics' Division of Biostatistics and Epidemiology) and Centers for Disease Control and Prevention (Vaccine Safety Activity, National Immunization Program). Representatives of both agencies oversee data processing and database management performed by a contractor.

VAERS receives 11,000 to 12,000 reports per year. Approximately 15 percent of the reports describe a ***serious*** event, defined as either fatal, life-threatening, or resulting in hospitalization or permanent disability. Selected reports of serious events and all reports of

[4] This proposed rule published in the *Federal Register* on September 23, 1997, 62 FR 49642.

fatalities are followed up individually by a health professional, and autopsy reports, as well as other medical records, are retrieved when available. Medical staff carefully monitor trends in adverse event reporting for vaccines, with particular attention to newly licensed vaccines. In addition to monitoring reports according to vaccine type, reports are monitored according to the vaccine lot.

Spontaneous reporting systems — for devices

Manufacturer and User Device Experience (MAUDE) Database

In 1984, FDA implemented the Medical Device Reporting (MDR) regulation, which required manufacturers to report device-related adverse events to FDA. In 1990, the Safe Medical Device Act (SMDA) amendments expanded FDA's authority by requiring that user facilities (e.g., hospitals and nursing homes) report device-related serious injuries to the manufacturer and device-related deaths to the manufacturer and directly to FDA. The Agency receives approximately 80,000 to 85,000 device-related adverse event reports every year. The bulk of the reports are from manufacturers, with user facilities submitting only about 5,000 of this total. The Manufacturer and User Device Experience (MAUDE) database, established in 1995 to support the SMDA, contains approximately 300,000 reports. Another 500,000 reports are in the pre-1995 database.

When received, reports are first triaged by medical professionals. In general, the criteria for taking action relate to the unexpectedness and seriousness of the event, the vulnerability of the population affected, and the preventability of the event. Reports that involve pediatric death, explosion, and/or multiple injuries from one device, are sent immediately to supervisors of the report review staff for evaluation and further action, if necessary. All reports are entered into the MAUDE database, subjected to a quality control procedure, and then sent to the clinical analysts for review within 48 hours of receipt. Clinical analysts review and assess the adverse event reports. Each analyst is responsible for products within a specific medical specialty or for products that have common design or material features. Here, as with drugs and biological products, the analysts' experience and familiarity with the products play a significant role in the evaluation of these reports.

Alternative Summary Reporting

To evaluate more effectively the large number of medical device

reports, FDA has initiated a risk-based alternative reporting system — ***summary reporting***. Products approved for summary reporting are well known with well-documented adverse event histories. This approach consists of the periodic submission of adverse event data in tabular format and provides significant economies for both the devices industry and FDA. In the past year, FDA received approximately 30,000 reports in summary format.

Additional surveillance approaches — for drugs and therapeutic biological products

Cooperative agreements and collaboration with the private sector are used to leverage FDA's internal expertise and surveillance data with formalized access to non-Agency epidemiologists and extensive databases. The goal is to have available, on relatively short notice, large, population-based databases to rapidly conduct studies to address safety issues of concern. The current agreement holders are discussed in Appendix C, along with some of the general characteristics of each database.

Access to healthcare databases

The FDA is a long-time user of the National Disease and Therapeutic Index (NDTI), the National Prescription Audit Plus (NPA), Provider Perspective (PP), and Retail Perspective (RP) for postmarketing surveillance activities.[5] The Agency is exploring the possibility of accessing LifeLink Medical Records Solutions database, and access to the United Kingdom's Mediplus database has been reviewed in a pilot effort. Using these databases, the Agency is able to access information, such as patient demographics, drug form and dosage use, drug dispensing trends, and retail pharmaceutical purchases. (See Appendix C.)

A wide variety of studies, initiated by signals from the spontaneous reporting systems, have been conducted by holders of cooperative agreements, including studies on antifungals and spontaneous abortion, antidepressants and suicide attempts, and the relative risk of hypoglycemia among diabetics following use of ACE inhibitors.[6] Frequently, these studies provide FDA reviewers with important epidemiological findings to support regulatory and labeling

[5] FDA accesses these databases through IMS Health Products and Services. Services are accessed in a number of ways including direct transfer from IMS's mainframe, through books, and using CD-ROM.

[6] Angiotensin converting enzyme inhibitors.

changes.

Registries for therapeutic products with unknown, but potentially serious, risks

Many products on the cutting edge of biotechnology are intended to treat life-threatening diseases and conditions. For these products, the level of acceptable risk can be fairly high. In some cases, there are potential risks to the population that extend beyond the individual patient receiving the therapy — risks that might not develop for months, years, or even decades. Examples include gene therapy and xenotransplantation. NIH maintains a registry of patients who participate in gene therapy studies. In addition, a national registry to follow up patients receiving xenotransplants has been developed. The xenotransplant registry will link the human recipient and the animal source to facilitate tracking should concerns about infectious disease transmission arise. Although these products are not being marketed currently, the registries established for investigational products will need to be continued once the products become available on the market.

Lot release and product testing programs

Because of the complex manufacturing processes for most biological products, each product lot undergoes thorough testing for purity, potency, identity, and sterility. Manufacturers may release lots only after this testing is documented. When necessary, FDA requires lot samples and protocols showing results of applicable tests to be submitted for review and testing by FDA. In this case, the manufacturer may not distribute a lot of the product until FDA releases it. The lot release program is a risk prevention measure that provides a quality control check on product specifications and also provides samples and documentation to permit follow-up investigations if safety issues arise. More than 7,000 lots are submitted for release each year. In addition to routine testing for lot release purposes, CBER laboratories test products and materials to investigate, evaluate, and follow-up on complaints and inspection findings.

Additional surveillance approaches — for blood, blood components, and blood derivatives

Interagency activities

Because blood safety is such an important public health issue, it is

the subject of ongoing interagency initiatives. FDA participates in a variety of cross-agency efforts including the Public Health Service (PHS) Advisory Committee for Blood Safety and Availability, the PHS interagency working group on blood safety — comprising representatives from National Institutes of Health, the FDA, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the Department of Defense — and the PHS Blood Safety Committee. These interagency groups have played a role in developing strategies to deal with emerging public health issues, risk assessment, blood safety issues, the Blood Action Plan, and plasma derivative shortage issues.

Additional surveillance approaches — for vaccines

The Vaccine Safety Datalink — a large linked database to study vaccine safety issues

Large healthcare databases linking medical interventions with outcomes provide the potential to improve the sensitivity of postmarketing safety surveillance programs. The Centers for Disease Control and Prevention has contracted with four large health maintenance organizations on the west coast to provide such databases for the investigation of vaccine safety issues. FDA staff collaborate on this project, and the Agency has contributed funding when available.

FDA has used the Vaccine Safety Datalink (VSD) to address a variety of concerns, some of which have arisen from VAERS reports. For example, an FDA review of adverse events reported in infants following receipt of hepatitis B vaccine revealed an apparent difference between two brands of this vaccine with regard to reporting rate (number of reports divided by number of doses distributed). Nothing in the product content or manufacturing processes provided a likely explanation for this difference. Because of the limitations of data in spontaneous reporting systems like VAERS, FDA believed it was essential to study this issue further before concluding that the difference was real. Data from VSD sites that had used both vaccines were reviewed. These data, which could provide a true event rate in a defined population, did not reveal a greater rate of adverse events reports for the suspect vaccine brand.

Interagency activities

Childhood vaccination is mandatory in most states, and large

numbers of healthy children are exposed to vaccines each year. Therefore, limiting the risks of vaccines is an important public health issue. Accordingly, vaccine safety is the subject of numerous initiatives within the Public Health Service, and FDA participates in a variety of cross-agency efforts in this area, including the Vaccine Inter-Agency Group coordinated by the National Vaccine Program Office, the Vaccine Safety Subcommittee of the National Vaccine Advisory Committee, and the Advisory Commission on Childhood Vaccines. FDA sends liaison members to other PHS agency advisory groups. These cross-agency groups played major roles in the ongoing development of the National Vaccine Action Plan and the Vaccine Safety Action Plan.

Varicella Vaccine Pregnancy Registry

In 1995, FDA issued a license to Merck and Co., Inc., to market Varicella Virus Vaccine Live for the prevention of chickenpox. Natural chickenpox can be dangerous for a developing fetus, and FDA anticipated inadvertent gestational exposures to this new, live virus vaccine. To address this concern, a pregnancy registry was established as an important component of safety surveillance for the vaccine. The accumulation of prospective data will support an objective assessment of possible risk attributed to this vaccine. The registry was collaboratively developed by the vaccine sponsors, the Centers for Disease Control and Prevention, and the FDA.

To date, the registry has recorded occasional congenital anomalies among fetuses exposed to the vaccine, but they appear to represent the numbers and types of adverse pregnancy outcomes that could be expected by chance, rather than due to the vaccine. The registry also serves as a source of information about the occurrence of medication errors. For example, several pregnant women who had been exposed to natural chickenpox were mistakenly given doses of vaccine rather than varicella zoster immune globulin (for passive immunization). These cases of product mix-up did not lead to evident harm, but their detection through the pregnancy registry provided FDA with an early warning about the need for improved educational efforts within the medical community to prevent additional errors. Cases will continue to be identified and followed via this registry for an indefinite period.

Additional surveillance approaches — for devices

Postmarketing surveillance studies

FDA's authority to require postmarketing studies for certain high-risk products is provided by the Safe Medical Device Act (SMDA) of 1990 as modified by the Modernization Act. A limited number of studies are currently being conducted under section 522 of the FD&C Act, Postmarket Surveillance. Numerous government, academic, and commercial databases have been identified that have been or could be used to conduct analyses of the safety of medical devices. (See Appendix C.)

Interagency activities

FDA collaborates with other agencies and organizations to address medical device problems, including the Centers for Disease Control and Prevention and the Consumer Product Safety Commission.

INITIATIVES UNDERWAY TO EXPAND POSTMARKETING RISK ASSESSMENT

Expanded postmarketing assessment

To reflect the increasing importance of postmarketing surveillance and risk assessment and to take into account the increased number of approvals each year, in the fall of 1998 the Center for Drugs expanded an existing division to create a new Office of Post-Marketing Drug Risk Assessment (OPDRA). The purpose of this new office is to plan, direct, and collaborate in the conduct of epidemiological studies to explore and confirm safety signals (see subsection below on safety signals), to assess risk, and to provide oversight for the monitoring of medication errors and other drug surveillance strategies. The staff is a multidisciplinary group of risk assessors and epidemiologists. One key task will involve identifying and assessing other databases that can be accessed to expand the Agency's epidemiological surveillance and regulatory impact studies.

Improved reporting

The under-reporting of adverse events and the often poor quality of data received from users are concerns shared by FDA's medical product Centers. Much of the data FDA receives do not allow a

complete understanding of the problems associated with an adverse event or allow the Agency to be proactive in protecting the public. Recently, FDA undertook a feasibility study to explore the barriers to reporting adverse events associated with the use of medical devices and to investigate various methods for overcoming those barriers. The working hypothesis of the feasibility study was that organizations well trained and educated in event recognition and reporting that receive support and feedback would be more likely to report events and also submit quality reports. Results of the study support the hypothesis. As already mentioned, the Modernization Act requires FDA to explore options for designing a national surveillance system based on a representative sample of medical device user facilities.

International activities

FDA participates in numerous international initiatives, such as those sponsored by ICH, to set global standards for medical product manufacturers to meet in the postmarketing regulatory setting. Similar initiatives are underway for medical devices through the Global Harmonization Task Force (GHTF). These initiatives are designed to reduce duplication of effort and improve the quality of data being submitted. These efforts will also improve risk assessment by decreasing data entry time and shortening the time to complete review.

Electronic safety reporting

The vast majority (90 percent) of suspected adverse events are reported by health professionals to pharmaceutical manufacturers, who in turn report the information to the FDA. The design concept for AERS incorporates the international standards (ICH) for content, structure, and transmittal of individual case safety reports. AERS also was designed to enable manufacturers to submit their reports of suspected adverse drug reactions electronically; the electronic capability is being implemented in a step-wise fashion. When fully implemented, AERS electronic access capability will help integrate reporting of postmarketing safety information worldwide and expedite detection of safety problems for marketed drugs.

In conjunction with AERS development and implementation, FDA's Center for Drugs and Center for Biologics are currently conducting a pilot program involving the electronic submission of periodic reports from pharmaceutical firms. The pilot program is designed

to develop and test the necessary processes, procedures, and technical architecture to implement the electronic submission of reports. This step-by-step program will help prepare for full-scale submission of reports in electronic format. The pilot initially included three major drug firms, and submissions were limited to one reporting form. To date, 13 firms have become involved in submitting test or production data. FDA has completed the initial phase of this pilot and now plans to expand the pilot to include additional manufacturers.[7]

OTHER EFFORTS BEING CONSIDERED TO EXPAND FDA'S POSTMARKETING RISK ASSESSMENT

Despite the number and variety of postmarketing risk assessment programs that FDA has initiated, the changing healthcare environment is challenging the Agency's efforts to rapidly identify, quantitate, and understand new risks associated with marketed products. As already discussed, the Agency is addressing some of these challenges. In some cases, areas have been targeted for expansion, but resources have not permitted the desired enhancements. Some of the targeted areas are discussed in the following sections.

Develop and improve automated systems

The FDA has been developing new systems to manage spontaneous reports for drugs, biological products, and devices, but additional work is needed. AERS, which is 14 months into operation, is just now beginning to achieve some of its goals. The MAUDE system will also need the types of analytical enhancements that are underway for AERS.

Expand systems integration

The Agency would benefit from increasing the integration of its current systems for reporting, monitoring, and evaluating adverse events and product defects. The level and types of integration that would provide the needed enhancements and efficiencies need to be evaluated carefully. Promising areas under exploration include sharing data entry, creating a common electronic gateway, and

[7] Full implementation and consequent fiscal savings to the Agency will take a requirement for manufacturers to submit adverse event reports to the Agency electronically.

sharing analytical techniques. The Agency is also considering establishing a shared data warehouse that would allow reviewers and researchers from any Center to investigate adverse event data using the same software. Database integration would improve the FDA's ability to assess adverse reports across Centers. Substantial efforts and resources will be needed to develop the integration proposed in these areas and provide accessibility to all reviewers and researchers.

Increase access to large healthcare databases

FDA's spontaneous reporting systems could benefit from increased access to broad-based health information databases that would allow the rapid exploration of potentially serious problems and more rigorous investigations than are currently possible. For example, a database maintained by a health maintenance organization will include usage data as well as event data, permitting estimations of incidence rates. Such estimations are impossible using only spontaneous reports, which provide no information on usage rates. The Center for Drugs and the Center for Devices have contracts with some health maintenance organizations for access to such databases, but these programs need to be expanded and made accessible to the entire Agency.

Create a network of sentinel sites

The creation of a network of sites (***sentinel sites***) would help provide optimal surveillance of products that are being used primarily at user facilities such as hospitals or clinics. A representative sample of these facilities could maintain full and accurate reporting of a reasonably high proportion of all adverse events that occur for a given product. For example, products used in organ transplant recipients could be monitored better if some organ transplant centers were identified and supported as sentinel sites. As noted earlier, this type of system is being piloted for medical devices. Under this plan, a network of designated hospitals would report on all device-related adverse events that occur at the sites. The pilot program has been limited by the cost of supporting such sentinel sites. The Center for Devices is now exploring how such as system could be expanded to include a representative sample of facilities.

Integrate pre- and postmarketing collaboration

Close communication and interaction among pre- and

postmarketing groups within the Agency would enhance the prospects of effective continuous surveillance as products move into the marketplace. Both the Center for Drugs, through its new Office of Postmarketing Drug Risk Assessment (OPDRA), and the Center for Biologics, through its Managed Review Procedures, have planned programs to encourage this type of interaction. Other Centers are considering similar approaches. For example, OPDRA is exploring the use of a tool that will allow some premarketing reviewers to view postmarketing safety reports in the aggregate.

Optimally, both premarketing and postmarketing staff should be actively involved in the design of postapproval studies and the analysis of observational studies submitted by sponsors in response to FDA postapproval requests. The availability of postmarketing data to premarketing reviewers considering additional indications for a currently marketed product would provide information on safety considerations for supplemental applications.

Achieving increased integration of pre- and postmarketing information will require additional staff, as it adds to the responsibilities of both premarketing and postmarketing reviewers.

Expand research

Adverse events

The Agency could enhance its ongoing programs by investing in research efforts designed to increase the understanding of the causes of and factors contributing to product-related injuries. The Agency needs more research on how to identify and report adverse events, how to provide healthcare professionals and consumers the right information to help them recognize and report on product-related problems, and how to improve analytical methods. The Agency also needs to investigate ways to focus more attention on medical products in the immediate postmarketing period.

Safety signals

A second area for research is expanding the Agency's ability to identify ***signals*** of potential safety problems from a database of spontaneous reports. Like the proverbial search for a needle in a haystack, the number and variety of reports, together with the number and variety of products and the lack of reliable usage information, make it difficult to distinguish variability and *noise* from a real concern. Only a small number of external statisticians

and epidemiologists are concerned with methods for screening and analyzing such databases. FDA has put some effort into developing improved tools to explore these databases so potential problems can be identified. Such efforts range from identifying new statistical methods, to establishing action thresholds, to developing computer software that primary report reviewers can use to screen the database for potential concerns. More work in this area is needed.

FDA's use of large-scale medical databases from health maintenance organizations and other sources for routine evaluation of product safety is in its infancy. Appropriate methods and software for analyzing these data are also needed, both for identifying signals and for doing follow-up investigations of signals identified elsewhere.

Backgound incidence rates

Another goal that will require large information systems in pharmacoepidemiology is to gain a better understanding of reporting rates by developing ***background*** incidence rates for problems in a population. For the relatively modest cost of conducting additional detailed chart reviews, product-related studies of a given syndrome could be extended to the descriptive epidemiology of the condition in the general population.

Product safety

Performing laboratory studies of approved products will help discover ways to enhance product safety. One example is the gene amplification (polymerase chain reaction) testing that is being performed on biological products to identify the presence of adventitious agents, such as the human immunodeficiency virus (HIV) and the hepatitis C virus. In another example, identifying surrogate biomarkers of toxicity has been identified by an internal review group of FDA scientists as a high-priority issue for the Agency.

Create Registries

The Agency is considering working with members of the healthcare community to create product registries. Discussions already have been initiated with the American College of Cardiology on the potential for a stent registry. FDA and the Centers for Disease Control and Prevention are exploring the possibility of establishing an independent registry center that manufacturers could contract to develop product registries when needed.

Amend existing statutes

FDA may want to work with Congress to change the FD&C Act to improve the Agency's ability to gather data on serious adverse events and move more quickly to mitigate their effects. One example might be to amend the FD&C Act so it contains the same suspension authority that is available under the Public Health Service Act. This would allow the Agency to suspend the marketing of medical products that present a danger to health, but that do not meet the imminent hazard threshold.

CONCLUSIONS, RECOMMENDATIONS, AND OPTIONS

To summarize, FDA currently employs a variety of postmarketing surveillance and risk assessment programs to ensure the continued safe use of medical products. Despite their dependence on the other participants in the overall risk assessment system, FDA's programs have been able to identify new risks and assess their impacts. However, recent regulatory changes, an increasingly complex healthcare environment, and the emerging global marketplace all present challenges to the existing system. As a result, the Agency has initiated a number of efforts to expand its programs to meet these challenges, including increasing the quality of reports, creating global reporting standards, and implementing electronic safety reporting. Increased resources are needed to support these ongoing efforts. In addition, a number of other options are available that could help the Agency meet the changing needs of the current system for postmarketing surveillance and risk management if resources could be made available. The options discussed in this Part are summarized below.

Recommendations

We recommend the Agency take the following actions:

- Rapidly complete the pharmaceutical products Adverse Event Reporting System (AERS), and enhance the medical device Manufacturers and User Device Experience (MAUDE) system.

- Integrate existing postmarketing information systems so analytic tools, data entry, and editing can be uniformly applied, and all information is readily available to every reviewer.

- Enhance and intensify surveillance of newly marketed products.
- Enhance clinical and laboratory studies to develop new methods to improve product safety.
- Develop new methodological tools for inference from available datasets.

Additional options

Additional options to improve postmarketing surveillance could include the following:

- Coordinate premarketing and postmarketing information to ensure full consideration of all available safety data at each stage of review.
- Supplement existing reporting channels by establishing and supporting institutions to serve as sentinel sites for adverse event reporting. Such sites would produce a higher rate of event reports and more completely analyze each event, further enhancing the value of their reports.
- Provide cross-agency access to external healthcare databases. This would allow the Agency to more quickly investigate signals generated by spontaneous reports and would be particularly valuable in determining the rate of adverse events.
- Design, implement, and maintain prospective product use registries (the bulk of support should come from manufacturers).
- Increase resources to conduct focused epidemiological studies when support of these studies by manufacturers is not feasible.
- Conduct methodological research in adverse event surveillance.

PART 4: MANAGING THE RISKS FROM MEDICAL PRODUCT USE

Parts 2 and 3 of this report describe the Agency's premarketing and postmarketing risk assessment activities for medical products. These programs serve to *identify* the risks of the product. Once risks are identified, the highest level of safety can be achieved only if those risks are *managed* appropriately. Part 4 of the report takes a look at the existing system for managing medical product risks. The Commissioner asked the Task Force to look into how the Agency relates to the other groups involved in these activities. As already mentioned, many groups involved in healthcare delivery are active in medical product risk management.

The discussion in Part 4 explores the need for a new systems framework for medical product use risk management that integrates the efforts of all involved parties. Recommendations and some options are listed at the end to provide a basis for future discussions with stakeholders on the design and implementation of such a new framework.

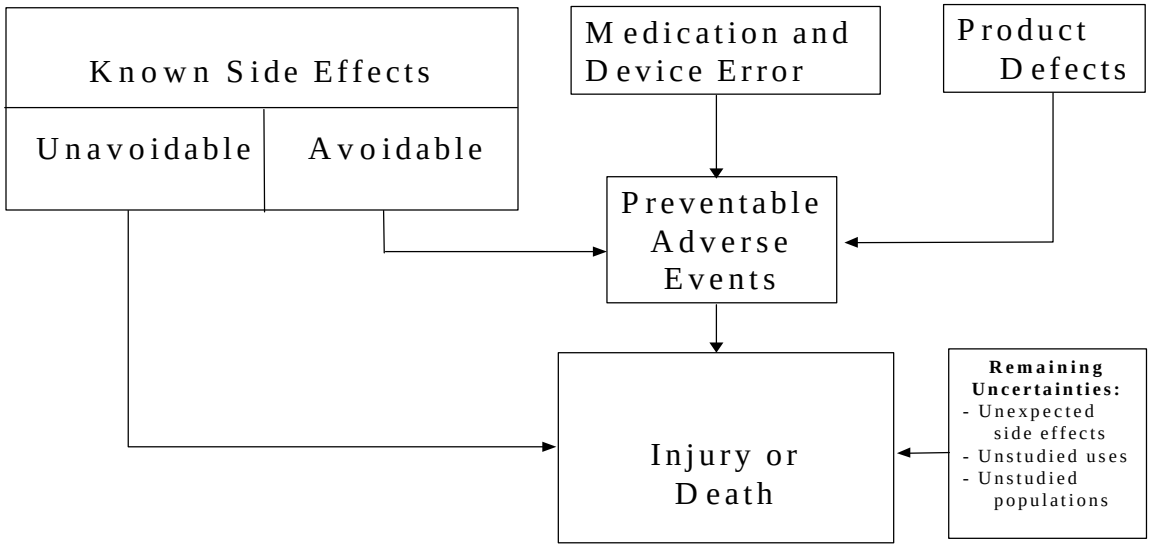
CURRENT RISK MANAGEMENT FOR MEDICAL PRODUCTS

Although marketed medical products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. All parts of the health care delivery chain try

to maintain this benefit-risk balance by making sure that products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk. The roles of each part of the healthcare system in product safety have evolved independently. Although each participant has a role in managing risks, no participant can be successful alone. Optimal safety can be accomplished only by an integrated system in which the roles and responsibilities, as well as capabilities and limitations, of each participant are known to all. Given the complexity of today's healthcare, our understanding of risk management must evolve from emphasis on the functions and responsibilities of freestanding groups (e.g., FDA, hospitals) to an understanding of product safety as a systems issue.

As discussed already in Part 1 and illustrated again below, recent concerns about the safety of medical products have focused on several types of risks, but often without distinguishing among the different types and their sources. Not all risks are the same. To effectively manage risks, it is necessary to identify the type of risk, the source, and the appropriate intervention. Each of the risks shown in the figure below needs to be managed differently, and by different components in an overall system.

Sources of Risk From Medical Products



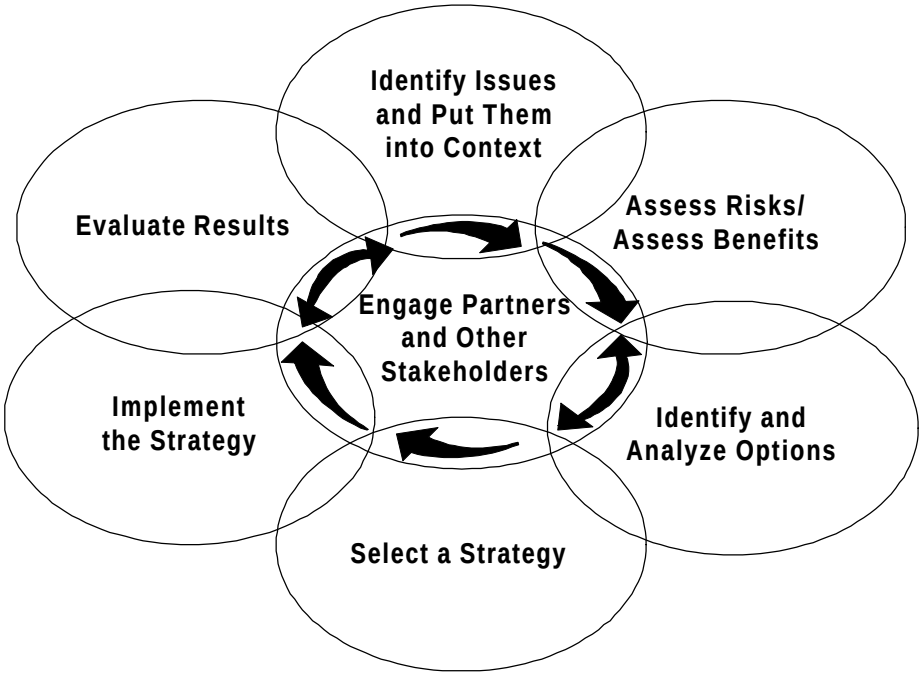
A conceptual framework for risk management activities is needed to focus discussion. As explained below, a specific framework has been developed for other health and safety issues within the Federal Government. This part of the report analyzes FDA's safety efforts within this risk management framework, and also points out the role of other participants, although their roles are not extensively explored. This benchmarking approach helps identify potential weaknesses in the overall system and areas for improvements or changes to FDA's approach. The discussion also sets the stage for the possible creation of an overall systems model of medical product risk management that incorporates the roles of all components.

FEDERAL RISK MANAGEMENT FRAMEWORK

In 1997, the Presidential/Congressional Commission on Risk Assessment published a report that included a proposed model for risk management.[1] The model for risk management encompasses processes for identifying and assessing the risks of specific health hazards, implementing activities to eliminate or minimize those risks, communicating risk information, and monitoring and evaluating the results of the interventions and communications. Because the processes identified in the model are consistent with the activities the Agency currently undertakes as part of its overall approach to risk management, the Task Force was able to adapt that model to the current system for managing risks from medical products. (See the proposed model below.) The activities included in the model are defined in the text box (Risk Management Activities) and discussed in more detail in the sections that follow.

[1] Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management — Final Report,* Vol. 1, 1997.

Proposed Risk Management Model



Efforts in risk assessment, intervention, communication, and evaluation occur at every level of the healthcare system. For unapproved products, FDA has the central risk management role. Access to unapproved products is usually limited to clinical trial settings in which safety is carefully scrutinized by investigators, manufacturers, FDA, and institutional review boards (IRBs). Part 2 of this report detailed manufacturer and FDA risk assessment activities in the preapproval period. For products of adequate quality, if FDA determines that a product's benefits outweigh its risks for a given use and population, the product is approved for marketing.

An activity often lacking in risk management models that needs to be included in any framework for managing the risks associated with using medical products is characterized as ***risk confrontation***: community-based problem solving that actively involves relevant

stakeholders in the decision-making process.[2] This activity has had lower priority than the Agency's premarketing and postmarketing risk assessment activities.

Risk Management Activities

Risk Assessment: estimation and evaluation of risk
Risk Confrontation: determining acceptable level of risk in a larger context
Risk Intervention: risk control action
Risk Communication: interactive process of exchanging risk information
Risk Management Evaluation: measure and ensure effectiveness of risk management efforts

Healthcare providers manage risk for their patients

Once products are approved, prescribers have the central risk management role. For prescription products, safety requires the participation of a learned intermediary, a highly trained practitioner whose role includes evaluating the risks and benefits for the individual patient and communicating them. Patients also frequently participate in risk management, weighing potential risks and benefits in light of their personal values. Other healthcare professionals, particularly nurses and pharmacists, have an important role in managing patient safety, particularly in risk communication activities.

Healthcare delivery organizations try to improve quality

Healthcare delivery organizations also have a major role in preventing injuries and deaths from medical products. Activities include interventions such as restrictions on the use of drugs or devices, requirements for professional training and credentialing, training efforts, quality assurance programs, and surveillance activities. Some hospital systems have risk management professionals who audit system performance.

[2] Leviton, L.C., C.E. Needleman, and M.A. Shapiro, *Confronting Public Health Risks: A Decision Maker's Guide*, SAGE Publications, Inc., 1998.

Many other organizations are involved

Today, many other organizations are involved in risk management as part of their role in improving the quality of healthcare. For example, in government, the Agency for Health Care Policy Research (AHCPR), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) issue medical practice guidelines, hold consensus conferences, and provide other communications intended to influence medical practice decisions. Government agencies involved in healthcare (the Health Care Financing Administration, the Veterans Administration, the Health Resources and Services Administration) also participate in risk management and the assessment of new technologies. In the private sector, many organizations, including professional societies, voluntary groups such as the American Medical Association's National Patient Safety Foundation, and consumer and patient advocacy groups, engage in a wide variety of risk management activities. A number of groups are involved in the prevention of medication errors. Effective risk management requires that all organizations act in partnership to assist healthcare providers in making appropriate practice decisions, and in ensuring that their decisions are properly carried out.

FDA has a role in postmarketing risk management

FDA's risk management role in the postmarketing period is primarily to make sure that accurate, up-to-date information is available to those managing risks and benefits. FDA does this by postmarketing risk assessment, regulation of advertising, and through its own communication efforts. However, even if the Agency carries out its role perfectly, the goal of achieving the safe use of medical products cannot be accomplished without effective partnerships with those who are actually managing the risks: healthcare practitioners, healthcare delivery organizations, and patients.

IS THE CURRENT RISK MANAGEMENT SYSTEM WORKING?

Recently, many critics have expressed the concern that the current risk management system is inadequate. The number of available medical products is rising rapidly and their complexity continues to increase dramatically. This growth in volume and complexity, fueled by the revolution in biomedicine, will continue. Physicians, pressed for time, struggle to keep up to date on the increasing flood

of available products. The potential for interactions among various treatments is also growing and is beyond the ability of most busy physicians to track. In addition, cost-containment actions, such as restricting formularies[3] and decreasing the duration of patient visits, taken by managed care organizations and third-party payers challenge physicians' ability to thoughtfully prescribe the medications with which they are most familiar.

Concurrent with these changes, the U.S. healthcare delivery system is changing significantly. The current emphasis on managing healthcare includes a focus on ensuring and measuring the quality of that care. One aspect of high-quality care is the ***appropriate use*** of medical products. The importance of this aspect of healthcare, combined with a recognition of the high human and economic costs involved, has resulted in new emphasis on an old problem: preventing injury and mortality from adverse events related to the use of medical products.

THE TIME IS RIGHT FOR A NEW SYSTEMS FRAMEWORK

Given the changing healthcare environment and the explosion of new products on the market, is the traditional system model for managing risks keeping pace? What would a new framework look like? What current and anticipated problems would a new framework have to address, and where are the opportunities for decreasing the number of serious adverse events?

Need for better data

A central obstacle to answering these questions is the lack of comprehensive data on the adverse effects from medical products. Although it is agreed that the aggregate burden created by serious adverse effects is enormous, detailed data are unavailable. What is the rate of adverse events in various settings (e.g., hospitals, outpatient care, nursing homes)? How many adverse events could have been prevented? How many are due to medication error? How many serious adverse events are unavoidable?

As detailed in Part 3 of this report, FDA is not funded, staffed, or in

[3] A *formulary* is a list of prescription drugs that a health plan has approved for use by its doctors. Health plans that have formularies develop their own unique lists of approved drugs. Health plans may only pay for medications that are on this approved list, unless the doctor goes through the health plan's Prior Authorization Process. Formularies may change at any time.

some cases authorized to collect such data. Most of FDA's postmarketing surveillance efforts are directed toward discovering new, unexpected adverse events. In recent years, the Agency has increased the evaluation of medication and device errors. However, FDA has not been extensively involved in the investigation of those risks that are expected in practice use. Although many organizations other than FDA have important roles in this area, no one group is charged with collecting comprehensive information that would delineate the scope of the problem.

Some have called for the establishment of an independent drug-safety board to expand and manage existing data systems, monitor and investigate safety problems, and make recommendations for solutions.[4] It is not clear, however, how such a board would fit into an overall system of safety.

Need for a systems approach

Experience in a wide variety of sectors, from pharmaceutical manufacture to airline safety, has demonstrated that the most effective way to get high-quality, consistent results in complex endeavors is to take a systems approach, rather than focusing on individual components. Many injuries and deaths resulting from medical products are preventable. This harm can be minimized through systematic risk management interventions. Although many organizations have developed the independent capacity to manage risk, synergistic efforts are needed to more effectively tackle this problem.

Need for an evaluation of the risk management system

In light of the widespread concerns about the risks incurred from using medical products, the Public Health Service (PHS), or other neutral body, should join in or convene a public forum with other public agencies and groups involved in healthcare to examine the current system of managing the risks from medical products. These forums should focus on the costs and value of better data on the incidence and causes of injuries from medical products and the roles of all stakeholders in risk management. The need for comprehensive data collection on the rates of the various types of adverse events could be a central point of discussion. The relative

[4] Wood, A.J.J., and R.L. Woosley, "Making Medicines Safer — The Need for an Independent Drug Safety Board," *N Engl J Med.*, 339:1851-1854, 1998.

magnitude and acceptability of the various types of risks could be examined, the risk management role of various components of the healthcare system evaluated, and opportunities for better controlling these risks explored. In particular, FDA could describe its role in the current system, as delineated in this report, and make suggestions for possible ways to enhance its risk management activities.

Subsequent to such a general meeting, FDA could meet with healthcare provider groups to further Agency partnerships in risk management and to develop a mutual understanding of their roles and of ways for creating a better system. Outcomes of these deliberations could be discussed at healthcare provider annual meetings or other events, thus providing broad input into the process.

These activities would constitute *systemic risk confrontation* — an evaluation by all stakeholders of the strengths and weaknesses of the current system. In addition to improving mutual understanding and suggesting system enhancements, these activities could help galvanize support for the information systems that will be needed in the future.

FDA'S OVERALL RISK MANAGEMENT ACTIVITIES

Although the FDA devotes considerable resources to its pre- and postmarketing risk assessment activities, the Agency has in recent years become much more active in other areas of risk management. This part of the report discusses FDA's programs within the current overall risk management system.

Risk assessment

Risk assessment includes the estimation and evaluation of a risk. FDA's premarketing risk assessment is intended to identify and quantify risks detected during clinical development and to evaluate how carefully any potential risks were assessed by the manufacturer. In addition, an evaluation of the risk of drug interactions as well as the potential for misadministration is performed. The known risks, along with any deficiencies in safety testing, are then weighed in the approval decision and described in the labeling of approved products. Part 2 of this report describes how the scientific and procedural quality of premarketing review of medical products is ensured.

Postmarketing risk assessment relies primarily on two modes of adverse event reporting to the Agency: spontaneous, voluntary reporting by health professionals and consumers, and mandated reporting by industry based on voluntary reporting to product manufacturers (plus user facilities in the case of medical devices, and physicians regarding specified events with certain vaccines.) As Part 3 of this report details, FDA's postmarketing systems are primarily focused on identifying new, unanticipated adverse effects that were not, or could not be, observed or recognized before marketing or that may arise due to medical use that was not anticipated. The Agency also receives and analyzes reports on medication errors.

In his 1978 book, William W. Lowrance defines something as safe if "its risks are judged to be acceptable."[5] Such a definition emphasizes the relativity of the concept of safety and implies that determining the safety of something requires not only measurement and assessment of its associated risks but also a judgment concerning the acceptability of those risks, in the context of the demonstrated benefits, to the population involved. A risk-benefit analysis is integral to FDA's review process for medical products: approval for marketing follows a determination that a product's benefits outweigh the risks associated with its labeled use for the intended population. The issue of the ***acceptance*** of known risks by the affected population is discussed below.

Risk confrontation

The National Research Council (1989) writes that determining the acceptable level of risk should occur in a larger context.[6] As described earlier, this activity is characterized as risk confrontation: community-based problem solving that actively involves stakeholders in the decision-making process.[7] This definition implies that social and community values are at least as important as the technical judgments of professionals and should be included in the determination of acceptable risk.

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[5] Lowrance, W.W., *Of Acceptable Risk: Science and the Determination of Safety*, William Kaufmann, Inc., 1976.

[6] National Research Council, *Improving Risk Communication*, National Academy Press, 1989.

[7] Leviton, *Confronting Public Health Risks*.

Traditional approaches to risk management assume that science and technology can measure the risks associated with the use of a medical product and quantify their significance. However, science provides only a statistical assessment of risk; it cannot determine its acceptability. Affected communities may differ from regulators in how they value either risks or benefits. They also may judge differently the amount of uncertainty that is tolerable. Advocacy groups for patients with various diseases, most notably AIDS and cancer, have taught us during the past several years that it is impossible to accurately assess the acceptability of risks in light of the potential benefits without the input of the affected community. Although some advocates for patients with life-threatening illnesses are willing to accept a high degree of risk to gain the benefits of new products, other advocacy groups, such as those against mandatory vaccination, feel that no risk is acceptable.

FDA is engaging stakeholders

To obtain community input, FDA has increasingly engaged its stakeholders in the regulatory process and developed partnerships with other Federal and non-Federal agencies when determining the acceptability of product risk. Some of these activities are discussed in the following pages.

Advisory committees

Discussion of premarketing applications with FDA advisory committees or device panels involves risk confrontation. The benefits and risks of a product are discussed, and frequently votes from the group are solicited. Not only are patient groups often represented on the committees or panels, but members of the public and interested groups are able to observe the proceedings and speak in the public sessions. The Agency may use these meetings to solicit recommendations on additional risk management approaches such as label warnings. Advisory committee or device panel meetings are sometimes held during the postmarketing period to obtain outside input on new risk information.

Collaboration and partnerships with stakeholders

FDA has developed alliances and collaborative relationships with health professionals, consumer and patient advocacy groups, industry organizations, and Federal and non-Federal agencies to gather information and advice during the assessment of product risks and benefits. Each Agency Center that approves human

medical products has established relationships or partnerships and developed programs to investigate risks, facilitate risk discussion and communications, and gain feedback about the risk-benefit assessment of medical products. (See examples in Appendix F.)

These risk confrontation activities exemplify some of FDA's best practices in risk confrontation, and they have been very successful. But they represent only a beginning. The Agency has not yet fully engaged stakeholders in the process for managing the risks incurred by using medical products. More community input is needed.

Risk intervention

Risk intervention is defined by the National Research Council as "the evaluation of alternative risk control actions, selection among them . . . and their implementation." [8] After the risks of a medical product are identified and assessed, they must be managed or minimized.

FDA makes the marketing decision

During the premarketing period, FDA is responsible for the ultimate action for managing risk: the marketing approval decision. If FDA decides that a product's risks outweigh its benefits, the Agency can prevent those risks by denying the product entry to the marketplace. Alternatively, if the Agency determines that a product's benefits exceed its associated risks, it grants marketing approval. After marketing, if new information changes the risk-benefit equation unfavorably, FDA can take a number of actions and can even initiate a product's withdrawal from the market.

FDA regulates product labeling

Another central FDA risk intervention activity is regulating the information in a product's labeling. The Agency must approve the original labeling, and review and approve most labeling changes. In addition, FDA regulates the advertising and promotion of marketed products. Promotional materials must not be false (i.e., must conform to the label and be substantiated), and they must not be misleading (i.e., they must be balanced and include the material facts). In great part, this means that benefits should not be exaggerated and that risks should be presented clearly. Regulation of labeling, promotion, and advertising is intended to ensure that

[8] National Research Council, *Improving Risk Communication*.

healthcare providers and consumers are adequately informed of the potential risks and benefits of a product, so that they can make decisions appropriate for each patient. In cases where medication error reports were made based on labeling problems, FDA has compelled the manufacturer to withdraw, repackage, or relabel the product. (See Appendix E.)

FDA engages in a number of other risk management activities

For products with specific risks, FDA may engage in a number of other risk management activities, such as mandating education for product users or limiting product distribution. Following are risk management activities currently undertaken by the FDA to manage risk associated with the use of medical products.

Additional restrictions on use

Occasionally, FDA may take special steps to limit risk directly. Restrictions on distribution (e.g., to specific hospitals or specialists) or requirements for practitioner qualifications or training may be imposed, or other restrictions on a specific product may be required. An example of such an intervention is the unprecedented effort the Agency took in restricting the use of thalidomide due to the product's potential to cause birth defects. Following extensive discussion of the sponsor's proposal for a fetal exposure prevention program, FDA approved thalidomide for the treatment of complications of leprosy and invoked regulatory authority to tightly control its U.S. marketing. The sponsor was required to develop a comprehensive oversight plan for the prescribing, dispensing, and use of thalidomide for physicians, pharmacists, and patients. (See Appendix F.)

Another example of restriction on use is demonstrated in the approval of a surgical transmyocardial revascularization device for the treatment of angina pectoris. In this case, the device was approved, but restricted to patients with severe symptoms who also provided written informed consent. For several other devices, including injectable collagen used to support the bladder in women with urinary incontinence, and excimer lasers for vision correction, FDA mandated that the products be provided only to practitioners specifically trained in their use. (For more examples of restrictions on use, see Appendix G.)

Postmarketing study requirements

Postmarketing studies can be used as risk management tools.

Under the accelerated approval regulations, FDA requires postapproval clinical studies after marketing to support continued product approval. In addition, FDA has the authority to require postmarketing studies as a condition of approval for high-risk devices. Although the Modernization Act repealed a mandatory postmarketing surveillance program for some high-risk devices, it gave the Center for Devices discretion to order a manufacturer to conduct postmarketing surveillance for any class II or class III device under certain conditions.[9] (See Appendix G.)

For drugs or biologics, FDA may obtain commitments from sponsors to conduct postmarketing studies if it determines further delineation of risks is necessary. For example, if there are concerns about how the safety findings in the clinical trials will relate to safety when marketed, the sponsor of the product may agree to conduct additional clinical investigations or epidemiological studies of the drugs in actual use (typically, phase-4 studies). Changes in the Modernization Act that require sponsors who have made postmarketing study commitments to report annually on the progress of the study should encourage the completion of these phase-4 studies.

FDA licensing of a vaccine for the prevention of chickenpox provides an example of such a phase-4 commitment. In this case, there were considerable concerns about the duration of immunity. In a commitment prior to licensing, the manufacturer agreed to conduct several postmarketing studies, including one 10-year study and two 15-year studies, to assess long-term immunity. (For more examples of commitments to additional studies, see Appendix G.)

Market withdrawal

Only the Secretary of the U.S. Department of Health and Human Services (HHS) may suspend the approval of a new drug application if there is an imminent hazard to the public health. This provision of the FD&C Act is cumbersome for use in an emergency and has been invoked only once. The only other route for nonvoluntary withdrawal of a drug product is quite time-consuming, requiring formal notices and an opportunity for a hearing. Therefore, the primary mechanism for removing risky

[9] The Center may do this if the failure of the device would be reasonably likely to have serious adverse health consequences; if the device is intended to be implanted in the human body for more than one year; or if the device is a life-sustaining or life-supporting device used outside a device user facility (section 522 (21 U.S.C. 360l) of the FD&C Act); see also Appendix G.A.2.

medical products from the market requires FDA to obtain ***voluntary*** agreement from the manufacturer. The FD&C and PHS Acts and Agency regulations provide a framework for manufacturers and distributors to follow when voluntary removal of marketed products is necessary. (See Appendix G.)

For devices, FDA has authority to mandate a recall if it concludes that there is a reasonable probability that a device intended for human use would cause serious adverse health consequences or death. Biological products are subject to mandatory recall provisions if a substantial or imminent hazard exists. FDA also has the authority to suspend or revoke a biological license.

The accelerated approval regulations (21 CFR 314.500-314.560 and 601.40-601.46) establish procedures for streamlining the medical product development and review processes for critically needed products without sacrificing good science and rigorous FDA oversight. FDA can approve a drug or biological product based on *surrogate endpoints* or markers.[10] Although these products can be approved more quickly, they must still meet legal safety and effectiveness standards. The regulation also establishes a streamlined withdrawal process if the postmarketing studies do not verify the product's clinical benefit, if there is new evidence that the product is not safe and effective, or if other specified circumstances arise. To date, this withdrawal portion of the regulation has not been invoked.

These examples illustrate some of FDA's risk management interventions. Because they have been successful, some critics have encouraged the Agency to become more proactive in risk intervention, more involved in the overall risk management system. Some critics have asked if the Agency shouldn't implement additional interventions.

Risk communication is a key component in risk managment

Risk communication is an interactive process of exchanging information related to risk. Effective risk communication facilitates

[10] A *surrogate endpoint* is a laboratory finding or physical sign that may not in itself be a direct measurement of how a patient feels, functions, or survives, but, nevertheless, is considered likely to predict therapeutic benefit. For a drug to be approved (given full marketing status) before trials that directly measure clinical outcomes are complete, there must be an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.

the exchange of information and helps affected parties make more informed decisions.

Within the historical framework of healthcare delivery, FDA's strategy for communicating risk information about approved prescription medical products has been to target the risk managers, that is, the physicians and other healthcare professionals. The primary communication tool has been the approved package labeling. Any risk-related information reported to the FDA subsequent to approval has traditionally been communicated primarily to healthcare providers through changes in a product's labeling information. However, in recent years FDA has sought more direct routes of communication and increased its communication with consumers and patients. Although FDA's current communication strategy, as described below, primarily consists of direct dissemination of information to the healthcare community and consumers, FDA is increasing those activities that promote a two-way ***exchange*** of information.

Product labeling

The product labeling, including the package insert, is revised and updated periodically by the manufacturer as new risk information becomes available. Healthcare professionals rely on the package insert for information on a product's known risks, benefits, and dosing information (or information for use) for the specific indications studied during clinical trials. In a recent FDA survey about how physicians use the product package insert, physicians responded that the Dosing and Administration, Contraindications, Warnings, Adverse Reactions, and Precautions sections of the package insert were most important.[11]

In 1979, FDA issued regulations extensively revising the organization of labeling, resulting in the eventual revision of the majority of product labeling. These changes included the addition and expansion of the Clinical Pharmacology section, a more structured organization of information on using the drug during pregnancy, and expanded information about adverse events. Since that time, FDA has continued to expand the content of the product package insert and provide more comprehensive information. For example, the presentation of adverse event information has become

[11] Ostrove, N.M., and L.A. Morris, "Use and Perceptions of Drug Product Labeling: A Survey of Physicians," unpublished manuscript, U.S. Food and Drug Administration.

more extensive due to improvements in detecting and collecting adverse events data during development. The insert also contains more descriptions and data from clinical trials that support the product's indications. More recently, information about using the product in pediatric and geriatric populations has been added.

Efforts are underway at the Agency to redesign the prescription drug and biological product package inserts so that healthcare professionals can access key prescribing information more readily. The design will be made available for public comment through a proposed rule.

When important new information emerges during the postmarketing period, methods in addition to package labeling revisions are used to communicate risks, primarily targeting the healthcare community. More recently, FDA has recognized the importance of communicating risk information about medical products directly to the public in a manner that is easy to understand. In some circumstances, information is communicated through the media or the Internet. For some pharmaceutical products, FDA requires the manufacturer to provide important patient counseling information in the Precautions section of the approved product labeling and encourages manufacturers to voluntarily provide patient package inserts that contain product risk information in consumer-friendly language. FDA has also asked manufacturers to provide patient package inserts for device products (e.g., for home use parenteral products).

Risk information for patients

Because communicating risk information to patients is important, FDA has tried for many years to ensure that patients receive patient labeling when they pick up their prescriptions. In August 1995, FDA proposed an increase in the dissemination of useful written prescription drug information for patients who receive prescription drugs on an outpatient basis. The next year, Congress passed a law requiring that the private sector be given the opportunity to develop a plan to reach the goals specified in the proposal. In January 1997, the Secretary of HHS accepted the plan. FDA continues to assess progress toward the year-2000 goal of at least 75 percent of people receiving useful written information with new prescriptions. By the year 2006, the goal is for at least 95 percent of people to receive such information.

FDA recently published a regulation that requires FDA-approved

patient labeling (*Medication Guides*) for drug and biological products that pose a serious and significant public health concern.[12] This regulation is expected to be invoked for a relatively small number of products (on average, between five and ten annually). (See Appendix G.)

Direct-to-consumer promotion

FDA ensures that promotional materials comply with regulations and include a balanced presentation of product benefits and risks (*fair balance*). For direct-to-consumer (DTC) promotional materials — through broadcast media, such as television, radio, or telephone — the risk information must be presented in a manner that is easily understood by consumers. DTC print advertisements are also required to have a summary of the risk information in the approved package insert (*brief summary*). These brief summaries appear on the back of advertisements in journals or consumer magazines. For DTC ads, FDA encourages manufacturers to present brief summaries in consumer-friendly language.

Outreach

Ensuring the widest possible distribution of new risk information is a major goal of FDA outreach. Historically, notifications produced by the Agency have included press releases, talk papers, meeting announcements, Safety Alerts, Public Health Advisories, articles, brochures, and Medical Bulletins. FDA staff members have also made numerous presentations on medical product safety at conferences and meetings in a variety of settings.

With advances in information technology, the Agency has begun using new avenues to reach target audiences. Websites maintained by FDA Centers and offices contain general and specific information for designated constituencies. This information includes product approval letters, package insert text, patient package inserts (when available), Dear Healthcare Professional letters, and information on product withdrawals and recalls. For example, FDA regularly posts notices of recalls and withdrawals of plasma-derivative products. At the urging of the National Hemophilia Foundation and other patient representative groups, FDA also began providing automated patient notification of these regulatory actions via e-mail.

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[12] This final regulation published December 1, 1998 (63 FR 66378), and will become effective on June 1, 1999.

When a significant safety-related regulatory action is taken, some notifications are sent automatically. Facsimiles (sent on the day information is issued) and periodic mailings of Agency documents are sent to major health organizations, healthcare agencies in other countries, congressional contacts, and consumer and patient advocacy groups. Over 140 health professional and industry organizations participate in the MEDWATCH Partners program, with each organization immediately notified (by Listserv e-mail or fax) of new material posted on the MEDWATCH website, a site specifically devoted to medical product safety. Each MEDWATCH partner disseminates this safety information to constituents, ensuring to the greatest degree possible that healthcare professionals and consumers have the latest risk information. A second MEDWATCH e-mail service, open to anyone who wishes to subscribe, provides immediate e-mail notification of new safety information.

The Agency is taking a proactive stance in getting information to those concerned, working directly with manufacturers on drafting Dear Healthcare Professional letters that they can disseminate. In certain circumstances (such as the issuance of a new boxed warning for a drug or a product recall involving a direct hazard to health), the Agency may arrange a conference call to appropriate health professional and consumer groups to inform them and solicit their input. In addition, supplementary question-and-answer sheets (Q & As) may be drafted and distributed.

FDA continues to look for ways to provide risk information about medical products as part of its ongoing effort to protect the public health. However, it is difficult to measure whether the information is effectively communicated (i.e., does the right information target the right audience at the right time). One specific improvement FDA will explore is the feasibility of making important communications look similar across the Centers. Although healthcare professionals, consumers, and patient groups have all stated that they want additional information and are encouraged by the Agency's efforts, the effectiveness of these communications in managing risk has never been systematically evaluated.

Today's environment of performance measurement demands that any system include an evaluation phase to monitor and ensure effectiveness. During the postmarketing phase, risk information is received and assessed by the FDA. This information is used to develop and implement risk management strategies and to formulate risk communication messages.

The Agency also uses this information to evaluate the effectiveness of some of its risk communications by, for example, monitoring changes in physician prescribing habits related to a product's adverse event rates. Communications about risk information (e.g., Dear Healthcare Professional letters and public safety alerts) can be effective in decreasing the number of prescriptions written, and often the rate of injury, as reflected by the frequency of such reports to the Agency. The Center for Devices routinely sends out a questionnaire concerning the safety alert/advisory to a random sample of recipients to evaluate its effectiveness.

However, even frequent communications may not always succeed in managing known, preventable risks. For example, until it was withdrawn from the market, some physicians continued to prescribe, and some pharmacists to dispense, terfenadine (Seldane) concomitantly with interacting medications, despite multiple warnings about potentially lethal interactions when using the drug with some other medications.[13] Overall, because of the lack of complete data on the causes and incidences of adverse events, evaluation of the effectiveness of some FDA interventions is difficult. (See Appendix I.)

CONCLUSIONS, RECOMMENDATIONS, AND OPTIONS

Conclusions

Medical products provide great benefit to the public, but they can also cause injury. FDA and the many other participants in healthcare delivery act to maximize the benefits and minimize the risks associated with using medical products, but often the actions of the participants are insufficiently integrated. The Task Force believes that the common goal of maximizing benefits and minimizing risks could be greatly advanced if the participants in the system worked together to gain an understanding of these activities within a systems framework. To achieve such a framework, we need a better understanding of the risks involved and their sources,

[13] Burkhart, G.A., M.J. Sevka, R. Temple, and P. Honig, "Temporal Decline in Filling Prescriptions for Terfenadine Closely in Time With Those for Either Ketoconazole or Erythromycin," *Clin Pharm and Ther*., 61:93-96, 1997. See also Cavuto, N.J., R.L. Woosley, and M. Sale, "Pharmacies and Prevention of Potentially Fatal Drug Interactions," *JAMA*, 275:1086, 1996.

and we need to clarify our individual roles and ensure that our individual roles are well integrated. Only then can we plan effective risk management strategies.

Key recommendation and options

The Task Force also identified a number of options for consideration, which, if adopted, might contribute to improved risk management. These ideas need full public policy analysis and review to understand their potential value, costs, and acceptability to the various stakeholders in medical product risk management. Some of the options would require significant new resources and legislative changes. Input from stakeholders on these options and their prioritization is needed. For these reasons, the Task Force's key recommendation is that:

- FDA join in or convene a meeting, or series of meetings, with stakeholders to discuss the current system for managing risks. As part of this meeting, FDA should consult stakeholders about the following options.

Options for improving risk confrontation

FDA should consider using risk confrontation more consistently and effectively in its risk management program. As the literature points out, accurately determining the acceptability of any risk requires that the stakeholders be engaged in the process. Although there has been increasing activity in this area, FDA needs to consider expanding its efforts to involve stakeholders in the risk management process. This could be achieved at several levels.

Systemic risk confrontation.

As discussed above, the Agency should consider convening or participating in meetings with all stakeholders to evaluate the current system and ways to improve it.

Product, indication, or class-specific risk confrontation

In addition to the above-described evaluation of the overall risk management system for medical products, the Agency could take a number of actions beyond risk assessment to improve its risk management efforts. For example, engaging stakeholders on the status of specific product, indication, and product class risks could be institutionalized at FDA (i.e., incorporated into the Agency's overall model of programmatic activities). Examples of possible

efforts include the following.

- Hold periodic FDA advisory committee meetings during which the *state of the armamentarium* for various indications is discussed and commented on by the advisors and the public

- Bring new risk information about approved products to advisory committees for discussion and public comment on a systematic basis

- Include reviews of currently available treatments during advisory committee meetings for specific products

- Develop ways to incorporate the views of patient groups into ongoing risk assessment, as has been done with the AIDS activists and the hemophilia community

- Expand partnership activities with other Federal agencies that perform health risk assessments (CDC, NIH, HCFA), and communicate on targeted disease/therapy areas, as has been done for breast cancer control and screening, vaccines, and blood and blood components

Options for improving risk interventions

The management of risks associated with using medical products, known as the *practice of medicine,* has traditionally been left in the hands of health professionals. The medical community historically has been reluctant to consider certain FDA actions that would limit practice decisions. In recent years, however, that community has increasingly accepted FDA decisions to restrict product distribution or mandate safety programs for risky products. In light of concerns about safety, the Agency could be assigned a more proactive role in risk management, particularly for medical products deemed to have higher-than-usual risks. Of course, adoption of any of the following options would require discussions with all stakeholders, and some of the options would require legislation or rulemaking to fully implement. Examples of possible actions include the following:

- Restrictions on distribution and/or use for certain products

- Mandatory education programs for prescribers and patients for certain products
- Restriction to certain use or prescriber category
- Identification of newly approved medical products that pose special risks
- Mandatory relabeling and/or reapproval of products within specific time period after approval
- Partnerships with Federal payers or accreditors to encourage appropriate prescribing and monitoring of specific drugs

Options for improving risk communication

FDA carries out extensive risk communication activities. However, these are not carried out in the context of an overall, systematic risk communication strategy. FDA could expand efforts to provide the primary risk managers and consumers with the right information, at the right time, in the right form. This means FDA would need the infrastructure to identify the important risks, target information to those who need it, and make sure it is available in a usable form. It also means that the effectiveness of these strategies would have to be continuously monitored.

FDA could consider developing a comprehensive risk communication strategy for medical products, including (1) categorizing the types and severity of risks and (2) tailoring communication activities based on the category of risk. For example, a risk identified as a serious drug interaction with a common nonprescription medication could trigger an Agency communication primarily to the general public, instead of the healthcare professional. To accomplish these goals, the Agency could use modern communications science to target appropriate audiences, shape messages, and choose communication avenues. FDA could use a variety of communication tools, such as the following :

1. Government-sponsored databases containing information that health professionals could access, including:

- Comprehensive information on drug-drug and drug-food interactions
- Registry information on the outcomes of the use of drugs during pregnancy

2. An expanded FDA website, to include:

   - Most recent package inserts
   - Product information sheets, data, and new product information
   - Consumer information including the most commonly prescribed medical products for specific conditions and new approvals
   - Possible links to other sites (e.g., new HHS National Guideline Clearinghouse)

3. Revised package insert format (this effort is in progress) with:

   - Health provider information that is easier to read and includes more information about the risks and benefits in the Patient Information section
   - Expanded patient-specific information and brief summary in lay language

4. FDA summary of drug approval information that would:

   - Describe remaining areas of uncertainty (e.g., long-term use or patients not studied)
   - Describe safety concerns, including different patient populations (pregnant women, pediatrics, elderly)

5. Template for Dear Healthcare Professional letters (FDA-wide or as appropriate for each Center) to make the process of risk communication more consistent that would:

- Provide a standard document to communicate important risk information in a clear manner

- Provide guidance on whether a Dear Healthcare Professional letter is needed, or whether another available communication mechanism (e.g., monthly labeling change summary, revitalized FDA Medical Bulletin) can be used

- Formalize time frames for requiring document to be developed and disseminated

6. Internal guidance to assess when Medication Guides need to be generated

7. Expansion of current partnerships with organizations, including:

   - Other Federal agencies (e.g., CDC, AHCPR, NIH, HCFA)

   - Healthcare organizations and agencies

     --Initiate clearinghouses for disease categories

   - Consumers and patient organizations

     --Establish relationships with health-related patient groups (American Association of Retired Persons, Arthritis Foundation)

   - Prescribers

8. Expansion of current efforts to educate public (outreach), including:

   - Develop PHS campaign on risk understanding

--Publish articles about assessing risks from medical products in consumer magazines (e.g., *Readers' Digest, Consumer Reports*)

--Run public health messages on TV about drugs and risks

--Partner with other public health agencies (to combine resources)

- Increase the circulation of *FDA Consumer* and improve content to send out targeted risk communication messages

- Talk to health groups at conferences and meetings

--Work with public affairs specialists in FDA field offices to reach and educate communities and constituents

9. Improved education of new healthcare professionals

- Work with medical schools and residency program directors to develop with FDA a teaching module on product development, approval, labeling, and risk communication to patients; have school curriculum incorporate this information

- Continue to support pharmacy internships and externship programs at FDA

- Provide training to healthcare professional groups

Options for improving evaluation of risk management

Better tools are needed to evaluate the effectiveness of FDA's risk management efforts. The lack of comprehensive epidemiological data on the scope of injuries from medical products makes outcome evaluation difficult. However, several steps could be taken to better assess the results of risk management activities.

1. Develop an *annual report card* for newly approved products. The report card would summarize newly learned risk information about the product and would provide an evaluation of how closely the predicted risks correspond to observed events.

2. Survey health professionals. FDA could consider conducting surveys of health professionals to determine whether risk information is being effectively communicated. Alternatively, sponsors could be requested to obtain such information.

3. Survey patients. FDA could consider patient or consumer surveys, possibly in partnership with patient or consumer organizations, to evaluate how well specific risk information is being communicated.

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ACRONYM LIST

AAO	American Academy of Ophtholomology
AARP	American Association of Retired Persons
AANN	American Association of Neurosciences Nurses
AANS	American Association of Neurological Surgeons
AAWG	Aggregate Analysis Working Group
ACG	American College of Gastroenterology
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
AHCPR	Agency for Health Care Policy and Research
AIDS	Acquired Immune Deficiency Syndrome
AMS	Aseptic Meningitis Syndrome
ANDA	Abbreviated New Drug Application
APhA	American Pharmaceutical Association
ASGE	American Society for Gastrointestinal Endoscopy
BCPT	Breast Cancer Prevention Trial
BPAC	Blood Products Advisory Committee
BSE	Bovine Spongiform Encephalopathy
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEF	Chick Embryo Fibroblast
CERTS	Centers for Education and Research on Therapeutics
CGMP	Current Good Manufacturing Practices
CIOMS	Council for International Organizations of Medical Sciences
CJD	Creutzfeldt-Jakob Disease
CNS	Congress of Neurological Surgeons
CSF	Cerebrospinal Fluid
CV	Cardiovascular
DAVDP	Division of Anti-Viral Drug Products
DIA	Drug Information Association
DOD	Department of Defense
DSMB	Data Safety Monitoring Board
DTC	Direct-to-Consumer
EIND	Electronic Investigational New Drug Aplication

EMEA	European Medicines Evaluation Agency
ENL	Erythema Nodosum Leprosum
ESTRI	Electronic Standards for the Transfer of Regulatory Information and Data
EU	European Union
EWG	Expert Working Group
FAO	Food and Agriculture Organization of the United Nations
FD&C	Federal Food, Drug, and Cosmetic Act
FOI	Freedom of Information
GAO	General Accounting Office
GHC	Group Health Cooperative
GHTF	Global Harmonization Task Force
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GPRD	General Practice Research Database
GRP	Good Review Practices
HCFA	Health Care Financing Administration
HGH	Human Growth Hormone
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IGIV	Immune Globulin Intravenous
IHS	Indian Health Service
IND	Investigational New Drug
ISMP	Institute for Safe Medication Practices
ISO	International Standards Organization
JAMA	Journal of the American Medical Association
JCAHO	Joint Commission on Accreditation of Health Care Organizations
MAPP	Manual of Policies and Procedures
MAUDE	Manufacturer and User Device Experience
MDR	Medical Device Reporting
MEDDRA	Medical Dictionary for Drug Regulatory Affairs
MERP	Medication Error Reporting and Prevention
MMR	Measles, Mumps and Rubella Vaccine
MMWR	Morbidity and Mortality Weekly Report

MRA	Mutual Recognition Agreement
MSSO	Maintenance and Support Services Organization
NACDS	National Association of Chain Drug Stores
NASPE	North American Society for Pacing and Electrophysiology
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCL	National Consumers League
NCPIE	National Council on Patient Information and Education
NDA	New Drug Application
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Inpatient Sample
NME	New Molecular Entity
NNMC	National Naval Medical Center
NPA	National Prescription Audit
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSAPB	National Surgical Adjuvant Breast and Bowel Project
NTDI	National Disease and Therapeutic Index
OA	Osteoarthritis
OBRR	Office of Blood Research and Review
ODAC	Oncologic Drugs Advisory Committee
ODE	Office of Drug Evaluation
OEA	Office of External Affairs
OHA	Office of Health Affairs
OPDRA	Office of Post-Marketing Drug Risk Assessment
OSB	Office of Surveillance and Biometrics
OSHI	Office of Special Health Issues
OTC	Over the Counter
PDUFA	Prescription Drug User Fee Act
PERI	PhRMA Education and Research Institute
PHA	Public Health Advisory
PhRMA	Pharmaceutical Research and Manufacturers of America
PHS	Public Health Service
PMA	Premarket Approval
PSC	Postmarket Strategies Committee
PSUR	Periodic Safety Update Reports
QA	Quality Assurance

Q&A	Question and Answer
QC	Quality Control
RA	Rheumatoid Arthritis
RSNA	Radiological Society of North America
SAMHSA	Substance Abuse and Mental Health Services Administration
SCVIR	Society for Cardiovascular Interventional Radiology
SMDA	Safe Medical Devices Act
SOPP	Manual of Standard Operating Procedures and Policies
SRS	Spontaneous Reporting System
SSED	Summary of Safety and Effectiveness Data
STAMP	Systematic Technology Assessment of Medical Products
STEPS	System for Thalidomide Education and Prescribing Safety
TSE	Transmissible Spongiform Encephalopathies
TSEAC	Transmissible Spongiform Encephalopathies Advisory Committee
TTTC	Take Time To Care
USP	U.S. Pharmacopeia
USUHS	Uniformed Services University of the Health Sciences
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organization

APPENDICES

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APPENDIX A

Comparison of Postapproval Risks for Drugs Approved Before and After the Implementation of PDUFA

INTRODUCTION

The drug review and approval process in the United States has undergone significant changes in the last few years. Complaints about FDA's drug approval process at the beginning of this decade challenged the length of time it took to get a product reviewed by the Agency. Some critics argued drugs were too often available in other parts of the world sooner than in the United States. With the implementation of the Prescription Drug User Fee Act (PDUFA) in 1992, the Food and Drug Administration Modernization Act of 1997, and Agency managerial initiatives, major improvements in review time have occurred for both priority and standard drugs. Several recent news articles have indicated a belief that the Center for Drugs is now approving drugs too fast, without having adequate safety information available at the time of approval.

The General Accounting Office (GAO) published a report, *FDA Drug Review — Postapproval Risks 1976-1985*, in April of 1990 that addressed safety concerns related to risks that were not uncovered until after drug approval and marketing. This allowed the Task Force to compare drugs approved during the PDUFA period with those of drugs approved in a prior time frame. Although the PDUFA program began officially in 1993, many drugs reviewed that year had entered the system pre-PDUFA. Thus, our study only looked at drugs approved during calendar years 1994 through 1997. Drugs approved in 1998 were not included since many of them have not yet been on the market long enough for unforeseen problems to have been identified and characterized. Both the GAO report and our analysis only looked at new molecular entities (NMEs).

This review had two goals: (1) to determine the rate of occurrence of serious postapproval risks in new drugs approved since changes in FDA review processes were made under PDUFA, and (2) to determine whether the rate of occurrence of serious postapproval risks in new drugs, as determined above, has changed since PDUFA became effective.

PROCEDURE

The supervisory consumer safety officers from the fifteen medical divisions were given a list of the 142 NME approvals during the period and asked to provide the following information:

1. A copy of the approved labeling at the time of approval
2. A copy of the current approved label
3. Copies of all Dear Healthcare Professional letters related to the drug

4. A summary of label changes that met the GAO criteria for serious postmarketing label changes based on the identification of significant postapproval risk (see discussion under Criteria)
5. Further details, if the drug was removed from the market due to serious postmarketing adverse events

One concern with this process was the fact that these products had not been on the market as long as the products studied in the GAO report. However, the GAO report states that "most unexpected adverse reports, particularly those that are serious, are expected to emerge within three years of approval." The GAO report did not specifically look at the time between drug approval and the first event leading to the identification of serious postapproval risk, so this statement cannot be verified.

GAO CRITERIA FOR A SERIOUS LABEL CHANGE

The criteria for assessing label changes were specified for each section of the drug label and are given in Table 1. If any criterion was met, the drug was classified as having a serious postapproval risk. The addition of a new indication, even though the inclusion of a new patient population might bring with it major risks for that group, was not included. The increase in risk had to be associated with the indication(s) for which the drug was originally approved.

Table 1
Criteria for Label Changes Reflecting Serious Postapproval Risk

Section of Label	Criterion for Serious Change
Description	None
Clinical pharmacology	None, although increased understanding of pharmacokinetics may reflect or lead to changes in other sections of the label.
Indications and usage	A limitation put on a drug's use or the removal of an indication because of adverse reaction reports' suggestion that use of the drug may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or to death. The limitation on use must correspond to the indications for which the drug was originally approved.
Contra-indications	The addition of a group of patients for whom the drug is contraindicated because it may lead to hospitalization or to increases in the length of hospitalization, severe or permanent disability, or death.
Warnings	The identification of a concern not listed in the original labeling, a much greater concern for a condition recognized before approval, or the addition of a subclass of patients (e.g., those who already have some serious illness or some other characteristic) for whom the drug may pose substantial danger that may lead to hospitalization, increases in the length of

	hospitalization, or severe or permanent disability or death.
Precautions	Changes that specify the need for increased diligence by the prescribing physician (e.g., in detecting underlying conditions or because of possible drug interactions that might pose a significant threat to the patient), the addition of a subsection providing information to alert the patient to watch for signs of a life-threatening adverse effect, or changes in other sections that are needed to forestall use of the drug that may lead to hospitalization, or severe or permanent disability or death.
Adverse reactions	The addition of newly identified adverse reactions with a high frequency or an increase in the frequency of previously identified adverse reactions to a high level that may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or death.
Drug abuse and dependence	None
Overdosages	The addition of overdose effects at recommended dosages that may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or death.
Dosage and administration	A reduction made to the recommended dosage because of concerns that a higher dose may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or death.
How supplied	None

RESULTS

During the 4 years studied, 142 NMEs were approved by the Center for Drugs. Of these drugs, two have been withdrawn from the market due to serious postapproval risks. Posicor (mibefradil dihydrochloride) and Duract (bromfenac), both approved during 1997, were withdrawn in June of 1998. One additional drug approved during the period, Redux (dexfenfluramine), has also been withdrawn from the market for safety reasons, but it is not included in the study because it was not a new molecular entity.

Posicor (mibefradil dihydrochloride), approved in August of 1997, is a calcium-channel blocker indicated for use in the treatment of patients with hypertension and chronic stable angina. Reports of serious adverse reactions after taking Posicor with several concomitant drugs led to label changes in December of 1997. The drug was withdrawn from the market by the manufacturer in June 1998 as a result of additional information about potentially harmful interactions with other drugs. Although in many cases drug interactions can be addressed by appropriate labeling changes and public education, the complexity of the prescribing information needed and the seriousness of side effects led to Posicor's withdrawal by the sponsor, Roche Laboratories.

Duract (bromfenac), approved in July of 1997, is a nonsteroidal anti-inflammatory drug (NSAID) approved for short-term management of acute pain (use for 10 days or less). It was never approved as a treatment for longer-term use for chronic conditions. In February 1998, following reports of severe liver failure, the warnings in Duract's labeling were strengthened with the addition of a black box and the sponsor, Wyeth-Ayerst Laboratories, issued a Dear Healthcare Professional letter. Despite these efforts, reports of severe injuries and death associated with liver failure continued to be reported with long-term use of Duract, leading to its withdrawal from the market in June 1998.

Table 2 gives the results of the review of the 142 NMEs approved in 1994-1997. It should be noted that all 24 products that had Dear Healthcare Professional letters also had label changes to reflect the safety concern. There were 19 products that had label changes that were considered serious, using the GAO criteria, that did not have an accompanying Dear Healthcare Professional letter. As should be expected, the numbers show a slight downward trend during the period, with an overall rate of just over 30 percent.

Table 2
Significant Label Changes for NMEs Approved in 1994-1997

Year	No Significant Label Changes	Significant Label Changes			Total NME Approvals	Percent of NME Approvals with Significant Label Changes
		Dear HC Professional Letter	No Dear HC Prof. Letter	Total		
1994	13	4	5	9	22	40.9%
1995	19	4	5	9	28	32.1%
1996	39	8	6	14	53	26.4%
1997	28	8	3	11	39	28.3%
Total	99	24	19	43	142	30.3%

It would seem likely that drugs approved under accelerated approval, which can be approved based on surrogate endpoints reasonably likely to predict clinical benefits, would have more changes as the required phase-4 studies are carried out. In the 4 PDUFA years, 11 drugs have been approved under this provision (see Table 2a). While this 54.6 percent rate is higher than the overall rate of 30.3 percent, the numbers are not large enough to influence the total results.

Table 2a
Significant Label Changes for NMEs Approved in 1994-1997 Under Accelerated Approval Provisions

Year	Priority			
	Yes	**No**	**Total**	**Percent**
1994	1	0	1	100%
1995	2	2	4	50%
1996	2	2	4	50%
1997	1	1	2	50%
Total	6	5	11	55.6%

Under PDUFA, priority drugs ─ those that appear to represent an advance over available therapy ─ have a 6-month review clock compared to a 12-month review clock for standard drugs. The results for the PDUFA years were examined to see if the decreased time for review might lead to more problems postmarketing. There has not been a significant difference in serious postapproval risk identification between these two categories of products. The results, given in Table 2b, indicate no difference between priority and standard applications except for 1994. This difference is due to both an increase in the rate of label changes for priority applications and to a smaller rate for the standard submissions.

Table 2b
Significant Label Changes for NMEs Approved in 1994-1997 (by Priority or Standard Submission)

Year	Priority				Standard			
	Yes	No	Total	Percent	Yes	No	Total	Percent
1994	7	5	12	58.3%	2	8	10	20.0%
1995	3	6	9	33.3%	6	13	19	31.6%
1996	5	14	19	26.3%	9	25	34	26.5%
1997	3	7	10	30.0%	8	21	29	27.6%
Total	18	32	50	36.0%	25	67	92	27.2%

COMPARISON WITH 1976-1985

The GAO report indicates that "a total of 209 new chemical entities" (name changed to *new molecular entities*) were approved during the 1976-1985 period, and their report addresses a total of 198 of the 209. They state that "of the 11 other drugs, four were never marketed; two were marketed for only a short time and then withdrawn, apparently for economic rather than safety reasons; two have not been marketed for some time and did not have up-to-date labels; and one was not considered a prescription drug. For the two other drugs, we were not able to obtain suitable labels for comparison."

Table 3, based on Table 3.6 of the GAO report, summarizes the results for 1976-1985 compared with those of 1994-1997. For the 10-year pre-PDUFA period, a total of 51.5 percent demonstrated postapproval increases in risk. The numbers of serious label changes per year during the period are highly variable and do not demonstrate a significant trend. However, a comparison of the first 5 years (1976-1980) with the last 5 years (1981-1985) of the GAO study do show a difference. The average for the first 5 years of the study is 58.5 percent and the average for the last 5 years of the study is 46.6 percent. Although it is likely that drugs approved in 1996 and 1997 will continue to experience additional label changes with continued use of the products, it is highly unlikely that the eventual overall rate for drugs approved under PDUFA will be as high as the 51.1 percent observed in the earlier products.

Table 3
Significant Label Changes for NMEs
Comparison of 1994-1997 Results With the 1976-1985 GAO Results

Year	No Significant Label Changes	Significant Label Changes	Total NME Approvals	Percent of NME Approvals with Significant Label Changes
1976	10	13	23	56.5%
1977	10	8	18	44.4%
1978	4	13	17	76.5%
1979	5	8	13	61.5%
1980	5	6	11	54.5%
1081	11	15	26	57.7%
1982	14	13	27	48.1%
1983	7	4	11	36.4%
1984	13	9	22	40.9%
1985	17	13	30	43.3%
Total 1976-1985	96	102	198	51.5%
1994	13	9	22	40.9%
1995	19	9	28	32.1%
1996	39	14	53	26.4%
1997	28	11	39	28.3%
Total 1994-1997	99	43	142	30.3%

Table 4, based on Table 2.1 of the GAO report, compares the significant label changes by Medical Category. Because of the disparity of the number of drugs within the various categories and the small number of drug products within many of the categories it is difficult to make direct comparisons.

Table 4
Significant Label Changes for NMEs by Drug Category
Comparison of 1994-1997 Results With the 1976-1985 GAO Results

Drug Class		1976-1985				1994-1997			
		No	**Yes**	**Total**	**Percent**	**No**	**Yes**	**Total**	**Percent**
101	Cardiac (1)	5	12	17	70.6%	4	2	6	33.3%
102	Antihypertensive-renal	9	6	15	40.0%	5	5	10	50.0%
201	Neurology	4	1	5	20.0%	9	2	11	18.2%
202	Psychopharmacological	6	9	15	60.0%	5	0	5	0.0%
203	Drug Abuse	2	3	5	60.0%	1	0	1	0.0%
301	Fertility-antifertility	2	3	5	60.0%	0	0	0	—
302	Metabolic-endocrine (1)	7	2	9	22.2%	10	3	13	23.1%
303	Metabolic-endocrine (11)	3	5	8	62.5%	7	0	7	0.0%
401	Antibiotic-systemic	7	18	25	72.0%	5	1	6	16.7%
402	Dermatologic	7	6	13	46.2%	7	0	7	0.0%
403	Anti-infective	4	2	6	33.3%	2	3	5	60.0%
404	Ophthalmic	3	3	6	50.0%	1	5	6	83.3%
405	Antiparasitic	2	2	4	50.0%	2	0	2	0.0%
501	Oncology	4	5	9	55.6%	13	3	16	18.8%
502	Radiopharmaceutical	11	5	16	31.3%	12	0	12	0.0%
503	Anti-inflammatory	3	11	14	78.6%	0	2	2	100.0%
601	Respiratory	5	0	5	0.0%	6	3	9	33.3%
602	Surgical	0	2	2	100.0%	0	0	0	—
604	Anesthesia	2	3	5	60.0%	3	1	4	25.0%
605	Renal	0	0	0	—	0	0	0	—
703	Anti-viral	0	0	0	—	3	9	12	75.0%

801	Cardiac (11)	1	0	1	0.0%	2	3	5	60.0%
803	Gastrointestinal	9	4	13	30.8%	2	1	3	33.3%
	Total	96	102	198	51.5%	99	43	142	30.3%

QUESTIONS RAISED BY THE STUDY

The GAO report did not address several questions that could provide potentially useful information. The first and most important question is whether or not there was a signal in the preapproval data submitted by the sponsor that should have alerted the Agency to the potential for trouble. A complete analysis would require going back through the original submissions for the products in detail, and would require far more resources than those available to the Agency. A corollary to this question would then be to consider if those same signals might have appeared in other applications that did not experience problems after marketing.

If signals are identified, it is still difficult to manage them. In some cases, indications of potential problems were seen during the review, and the product was labeled to alert healthcare practitioners of the potential for problems. This attempt to forestall postapproval events through warnings in the label has had mixed success. For example, Duract was clearly labeled to be used for no more than 10 days because of elevated liver enzymes observed in the trial. Despite the addition of a black box warning after reports of liver failure began to come in, the drug had to be withdrawn from the market.

The second important question that was not asked by the GAO report was how soon after the approval of a product the potential for serious postapproval risk was identified. This information might help to determine how much time is necessary postmarketing, on average, before our knowledge of the risks of a drug begins to stabilize. We will not be able to examine this question for the PDUFA cohort of drugs for another 3 to 5 years.

CONCLUSIONS

This examination of the cohort of NMEs approved during the PDUFA period gives confidence that the postapproval identification of serious drug risk has not increased, despite several factors that have led to an increase in the reporting of postmarketing adverse events to the agency. In fiscal year 1997, the Center for Drugs received 254,841 reports of suspected drug-related adverse events, compared with 51,188 in 1988. Part of this increase is due to the FDA's MEDWATCH Program. MEDWATCH, launched in 1993, solicits adverse drug reports from individual healthcare practitioners and makes it easier to submit them. Most suspected adverse event reports continue to come from manufacturers' periodic reports, but individuals submitted 12,453 direct reports to FDA in 1997.

It does appear from the data collected that the number of Dear Healthcare Professional letters has gone up in recent years. Healthcare providers are requesting more information and more timely

information, and consumers are beginning to join them. Furthermore, with the advent of direct-to-consumer advertisements in magazines and on television, consumers are more aware of the availability of new drugs and also the potential risks of those drugs. These trends should lead to the identification of potential problems in a more timely manner.

RELATION OF FDA'S PREMARKET QUALITY SYSTEMS TO ISO 9001:2000

ISO 9001 is a generic, worldwide quality management system standard promulgated by the International Organization for Standardization (ISO). ISO is currently completing a revised edition of this standard, ISO 9001:2000.

ISO 9001:2000 sets forth the quality management system requirements an organization should have in place to demonstrate its capability to meet customer (stakeholder) needs. The process-based structure envisioned by ISO 9001:2000 is built around four key areas of concern:

- Management responsibility (policy, objectives, planning, quality management system, management review);
- Resource management (human resources, information, facilities);
- Process management (customer satisfaction, design, purchasing, production); and
- Measurement, analysis, and improvement (audit, process control, continual improvement).

The ISO framework does not impose uniform quality management systems, but instead provides criteria by which an organization can ensure that its products and services conform to customer requirements. FDA has wide public health responsibilities, and its premarket review systems seeks to meet the needs of the public, industry, and healthcare professionals. The creation and application of a comprehensive quality system helps ensure FDA's premarket review systems meet these public health responsibilities.

FDA mapped its premarket review quality systems functions against the ISO 9001:2000 framework to ensure that they cover all essential elements necessary to ensure stakeholder needs are understood and met. The following outline provides an overview of FDA's approach. CBER, CDER, and CDRH each prepared detailed a inventory of the procedures and processes that met each element in the outline.

1. Management Responsibility

- 1.1 General
- 1.2 Customer Needs and Requirements
- 1.3 Quality Policy
- 1.4 Quality Objectives and Planning
- 1.5 Quality Management System
  - 1.5.1 SOPs for Administrative Record of Review and Decision
  - 1.5.2 Procedures to Validate and Control Changes in Policy
  - 1.5.3 Records Retention Criteria and Archiving Procedures
- 1.6 Management Review

2. Resource Management

- 2.1 General
- 2.2 Human Resources
  - 2.2.1 Provision of Adequate Staff
  - 2.2.2 Staff Qualifications
    - 2.2.2.1 Education
    - 2.2.2.2 Experience
    - 2.2.2.3 Program Orientation
    - 2.2.2.4 Core Competency program.
  - 2.2.3 Continuing Education to Ensure Currency of Staff Qualifications
  - 2.2.4 Assignment of Appropriate Staff (Skills) to Review Teams
    - 2.2.4.1 Written Procedures for Selection of Team Members, Including Supervisory Concurrence
- 2.3 Other Resources (Information, Infrastructure, Work Environment)
  - 2.3.1 Adequate Office Space, Supporting Infrastructure
  - 2.3.2 Document Storage and Retrieval, Both Physical and Electronic
  - 2.3.3 Network Communication, Document Retrieval, Information Exchange
  - 2.3.4 External Information
  - 2.3.5 Library
  - 2.3.6 Supplies

3. Process Management

- 3.1 General
- 3.2 Customer-Related Process
- 3.3 Design and Development
  - 3.3.1 Design of, or Changes to, Review Process are Evaluated Against Customer Needs and Function
  - 3.3.2 Development and Application of Review Standards
  - 3.3.3 Marketing Application Content Design
    - 3.3.3.1 Content Regulations

3.3.3.2 Documents on Agency Policy
3.3.3.3 Communication with Applicant During Data Development Process
3.4 Purchasing
3.5 Production and Service Operations
3.5.1 Advisory Committee Input
3.5.2 Structured Advisory Committee System
3.5.2.1 Controls of Potential Conflicts of Interest
3.5.2.2 Inclusion of Public / Industry Views
3.5.3 Criteria for When Advisory Committee Input is to be Sought
3.5.4 Maintenance of Record of Review and Recommendation
3.5.5 Product Jurisdiction Determination Criteria, Regulations, Staff
3.5.6 Written SOPs for Review Processes
3.5.6.1 Consultation Procedures, Both Within the Agency and With Other Federal Agencies
3.5.6.2 Standing and Ad Hoc Policy Committees to Consult and Advise Concerning Novel or Difficult Review Issues
3.5.7 Procedures for Resolving Internal Differences in Scientific Judgment
3.5.7.1 Review Team Concurrence, Minority Views
3.5.7.2 Internal Ombudsman and Dispute Resolution Procedures
3.5.8 Structured Supervisory Rereview, Final Decision
3.6 Control of Nonconformity
3.7 Post Delivery Services

4.0 Measurement, Analysis, and Improvement

4.1 General
4.2 Measurement
4.3 Analysis of Data
4.4 Improvement
4.4.1 Systematic Examination of Failed Products and Factors Affecting Failure to Recognize Failure Mode During the Initial Development and Review Processes
4.4.2 Periodic Review of *Normal* Decisions to Ensure Consistency and Application of Appropriate Decision Criteria

APPENDIX B

Examples of Legislation, Regulations, and Guidance for Industry Related to Postmarketing

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The following are examples of legislation, regulations, and guidance for industry that relate to the Agency's postmarketing efforts. This is not intended to be a complete listing of related documents.

Legislation

Federal Food, Drug, and Cosmetic Act, 21 U.S.C. Sections 201 et seq.

Safe Medical Devices Act of 1990 (SMDA). Introduced requirement for Medical Device Reporting (MDR) by User Facilities (effective 11/28/91) and Domestic Distributors.

Medical Device Amendments of 1992 (MDA). Provided FDA with authority to require reports for adverse events deemed "significant adverse device experiences."

Food and Drug Administration Modernization Act of 1997, effective February 19, 1998.

Regulations

21 CFR 310.305 – Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

21 CFR 312.32 – Investigational new drug (IND) safety reports

21 CFR 314.80 – Postmarketing reporting of adverse drug experiences

21 CFR 600.14 - Reporting of errors (Biologics)

21 CFR 600.80 – Postmarketing reporting of adverse experiences (for licensed biological products)

21 CFR 600.81 – Distribution reports (for licensed biological products)

21 CFR 610.2 - Requests for samples and protocols; official release

21 CFR 803 - Medical device reporting

21 CFR 804 - Medical device distributor reporting

Federal Register Notices

Form for Reporting Serious Adverse Events and Product Problems With Human Drug and Biological Products and Devices; Availability (MEDWATCH) (58 FR 31596) June 3, 1993.

Final Rule: Medical Device Distributor Reporting. Collection requirements for all wholesale distributors (including importers) codified in 21 CFR 804, September 1, 1993.

Final Rule: Medical Device User Facility and Manufacturer Reporting, Certification and Registration (effective date 4/11/96). Revised final reporting requirements for manufacturers and user facilities under SMDA and MDA, including requirement for use of 3500A form, December 11, 1995.

Final Rule (Extension of Effective Date): Medical Devices; Medical Device User Facility and Manufacturer Reporting, Certification and Registration; Office of Management and Budget Approval; notification of approval of information collection requirements (extended effective date to 7/31/96 for final regulation) (61 FR 16043), April 11, 1996.

Final Rule (Stay of Effective Date; Revocation): Medical Devices; Medical Device Distributor and Manufacturer Reporting; Certification, Registration, Listing, and Premarket Notification Submission; changes to annual certification and U.S. designated agents (61 FR 38345), July 23, 1996.

Final Rule (Stay on Requirement for Denominator Data): Medical Devices; Medical Device Reporting; Baseline Reports; Stay of Effective Date, (61 FR 39868), July 31, 1996.

Final Rule (Revoked Requirement for Increased Frequency Reports as Expedited Reports Because These Reports Have Not Contributed to Timely Identification of Safety Problems), Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports (62 FR 34166), June 25, 1997.

Direct Final Rule and Proposed Rule (Revised 21 CFR 803 in accordance with changes under the Modernization Act and moved requirements for importers and distributors from 21 CFR 804 to 21 CFR 803): Medical Device Reporting: Manufacturer Reporting, Importer Reporting, User Facility Reporting, and Distributor Reporting (63 FR 26069), May 12, 1998.

Direct Final Rule (withdrew final rule published May 12, 1998, due to significant comment): Medical Device Reporting: Manufacturer Reporting, Importer Reporting, User Facility Reporting, Distributor Reporting (63 FR 45716), August 27, 1998.

Agency Information Collection Activities; Proposed Collection; MEDWATCH: The FDA Medical Products Reporting Program; Comment Request (proposed revision of MEDWATCH Forms 3500 and 3500A to incorporate new data elements) (63 FR 63064), November 10, 1998.

Guidances for the Center for Drugs and the Center for Biologics

Postmarketing Reporting of Adverse Drug Experiences (March 1992)

Postmarketing Reporting of Adverse Experiences - Biologics (October 1993)

Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products Clarification of What to Report (August 1997)

Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations (August 1997)

How to Complete the Vaccine Adverse Reporting System Form (September 1998)

Guidances for Devices

Overview of FDA Modernization Act of 1997 (March 11, 1998)

Medical Device Reporting for Manufacturers (March 1, 1997)

Medical Device Reporting for User Facilities (April 1, 1996)

Medical Device Reporting: An Overview (April 1, 1996)

Medical Device Reporting for Distributors (April 1, 1996)

Instructions for Completing Form 3500A with Coding Manual for Form 3500A (December 15, 1995)

Remedial Action Exemption - E1996001 (July 30, 1996)

Breast Implant - E1996002 (August 7, 1996)

Needlestick and Blood Exposure - E1996003 (August 9, 1996)

Intraocular Lenses - E1996004 (August 7, 1996)

Variance from Manufacturer Report Number Format - MDR Letter (July 16, 1996)

Variance from Manufacturer Report Number Format (Variance 5) (August 12, 1996)

International Conference on Harmonisation Guidances

The purpose of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is to recommend global standards that pharmaceutical manufacturers can follow when dealing with regulators to reduce duplication of effort and focus on the safety and efficacy of their products. Five safety-relevant ICH expert working groups met through 1998 and have issued their final guidances, which FDA is now implementing.

E2A *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1, 1995)

E2B *Data Elements for Transmission of Individual Case Reports* (March 1, 1995)

E2C *Clinical Safety Data Management: Periodic Safety Update Reports* (May 19, 1997)

Modernization Act Guidances For Devices

Guidance for Industry, Review Staff, and the Clinical Community – issued November 21, 1998

Guidance Procedures to Determine Postmarket Surveillance Strategies – issued February 2, 1998

Guidance on Procedures for Review of Postmarket Surveillance Submissions – February 19, 1998

Safe Medical Devices Act (SMDA) to FDAMA: Guidance on FDA's Transition Plan for Existing Postmarket Surveillance Protocols – July 22, 1998

APPENDIX C

Cooperative Agreements and Collaborative Resources

IMS HEALTH

The FDA is a long-time user of IMS Health products and services. This includes IMS's National Disease and Therapeutic Index (NDTI) and National Prescription Audit (NPA).

FDA primarily uses IMS's NDTI and the NPA for postmarketing surveillance activities. The NPA provides national estimates of prescription drug use in the United States based on data collected from over 20,000 computerized retail, chain, grocery, and mail-order pharmacies nationwide. These data can be used to track prescribing trends over calendar time and for calculation of adverse drug reaction (ADR) reporting rates. The NDTI database provides information on the age and gender distribution of patients using outpatient drug products, as well as information on the duration of treatment course and indication for use. These large population-based databases have application in a variety of areas, including hypothesis testing, signal refinement and/or confirmation of signals emerging from spontaneous case reports. In addition, they may also be used to assemble case-series and retrospective cohort and/or case-control studies to estimate relative risks and identify important risk factors.

Drug exposure is reported as number of outpatient prescriptions. It can be trended over calendar time, and stratified by age, gender, and indication for use. When used in conjunction with supplemental data obtained from population-based claims or record-linked databases, it is possible to estimate the actual number of patients exposed to a drug product. These data are used in association with spontaneous case reports data to understand the context within which ADRs occur. Potential uses of this data could include patterns of drug usage, patterns of concomitant drug usage, and/or trends in drug usage.

Examples of Cooperative Agreement Utility

Routine collaborative use has been made of IMS Health to support regulatory actions by the Center for Drugs and a variety of other users.

- Used extensively in the review of terfenadine prior to its withdrawal from the market
- Used routinely to evaluate effect of prescription-to-OTC switches
- Used to evaluate Diprivan (propofol), a generic drug marketed with a different preservative from the innovator product

- Used to provide data regarding schedule II and other drugs with abuse potential for use in determining manufacturing quotas

- Used to provide sales figures to support cost/benefit arguments for PDUFA II. Demographic data has been used to provide support decisions concerning the Medicare formulary

- Used in providing demographic patterns of use in support of congressionally-mandated initiatives to encourage study in various subpopulations.

The Center for Biologics Collaborative Resources

The Vaccine Safety Datalink (VSD) – This is a large linked database that studies vaccine safety issues. The availability of large healthcare databases with medical interventions linked with outcomes provides the potential for substantial improvements in the sensitivity of postmarketing safety surveillance programs. The Centers for Disease Control and Prevention (CDC) has contracted with four large health maintenance organizations on the West Coast to provide such databases for the investigation of arising vaccine safety issues. FDA staff have served in an advisory capacity for this project and the Agency has contributed funding when available.

VSD has been used to address a variety of concerns, some of which have arisen from the Vaccine Adverse Event Reporting System (VAERS) reports. As an example, an FDA review of adverse events reported in infants following receipt of hepatitis B vaccine revealed an apparent difference between the two different brands of this vaccine with regard to reporting rate (number of reports divided by number of doses distributed). Nothing in the product content or manufacturing processes provided a likely explanation for this difference. Because of all the limitations of data in spontaneous reporting systems like VAERS, it was felt essential to study this issue further before concluding that the difference was real. Data from VSD sites that had used both vaccines were reviewed; these data, which were more reliable than those from VAERS in that they could provide a true event rate in a defined population, did not suggest any increased reactogenicity of the suspect vaccine brand.

Limitations of the VSD include the fact that not all outcome data are automatically captured. For example, deaths occurring at home or outside the HMO system are not generally recorded. Substantial effort is required to prepare an analysis dataset from the raw data provided by the clinics to study a specific question, so rapid response to a pressing issue is usually not feasible. The VSD population is probably not sufficiently representative of the U.S population, which has implications for investigation of issues that may be specific to a geographic region. For example, the VSD does not provide an optimal population for follow-up studies of Lyme disease vaccines. Many of these problems can be diminished in principle, and the CDC has been actively pursuing the additional resources required to enhance the capability of the VSD.

The Center for Drugs Collaborative Resources

Cooperative Agreement Program

The Office of Post-Marketing Drug Risk Assessment (OPDRA) leverages its internal expertise and surveillance data with formalized access to extensive databases and epidemiologists (principal investigators) experienced with the use of each database. The following are the current agreement holders working with FDA under the Cooperative Agreement Program:

1. United Health Care – Serves more than 40 million individuals through a broad continuum of healthcare products and specialty services. Current and historical medical and pharmaceutical data from 12 health plans are included in the research database, covering about 2.1 million lives. This database comprises more than 13.1 million member years of data since 1990.

2. Harvard Pilgrim Health Care – The Joint Pharmacoepidemiology Program combines populations and resources from three HMOs – Harvard Pilgrim Health Care, Boston; HealthPartners, Minneapolis; and Fallon Community Health Plan, Worcester, Massachusetts. Each HMO maintains automated record linkage systems, including drug dispensing information, coded diagnoses for ambulatory and inpatient care, and access to medical records. Combined current membership is in excess of 2 million.

3. Vanderbilt University – This database contains data from Tennessee Medicaid, a joint federal-state program that finances medical care for qualifying low income patients. In 1997, Tennessee Medicaid had approximately 1.4 million enrollees, 500,000 children under 15 years of age, 150,000 persons over age 65, 400,000 African-Americans, and 35,000 births annually. Computerized files of the Medicaid program – which include enrollment, pharmacy, hospital, outpatient, and nursing home files – define the population and patient time, provide a measure of drug exposure, facilitate rapid disease ascertainment, and provide some information on confounders.

4. Boston Collaborative Drug Surveillance Program – The General Practice Research Database (GPRD) provides information derived from computerized general practices in the United Kingdom and Group Health Cooperative (GHC) of Puget Sound (recently merged with Kaiser Northwest, creating potential access problems with current data). GPRD provides relevant information on 4,000,000 patients in the United Kingdom. GHC has maintained computer files for 325,000 patients since July 1976, as well as discharge diagnoses in excess of 400,000 from hospitalizations since 1972.

5. Johns Hopkins University – The Johns Hopkins AIDS service is the largest care provider for HIV/AIDs infected persons in Maryland. In 1992 a comprehensive longitudinal, observational database was launched through funding from the Maryland Department of Health and Mental Hygiene and the Agency for Health Care Policy and Research (AHCPR). Currently the database represents over 3,500 patients from January 1990 through the present and is fully linkable with other Johns Hopkins Health Systems.

The Center for Devices Collaborative Resources

1. IMS America Hospital Supply Index

This database contains estimates of medical surgical products in 1500 product categories purchased by 350 hospitals in the United States. This data can be used to derive comprehensive estimates of product purchases and device sales. However, the data do not allow analysis of user characteristics, and devices purchased but not used are not accounted for.

2. Nationwide Inpatient Sample (NIS)

This database is a stratified probability sample that approximates 20 percent of the U.S. community hospitals. Records include all inpatient hospital stays, patient demographic characteristics, diagnosis, procedures, length of stay, and patient status. Information from this database can be used for national estimates and is particularly good for research on implantable devices. These data are not current and cover inpatient hospital stays only.

3. Medicare Data

Medicare data are available from the Health Care Financing Administration (HCFA). This hospital insurance information contains data on inpatient hospitalizations, hospice, home health, and skilled nursing care. The supplementary medical insurance data files contain information on physician services, outpatient visits, durable medical equipment, and home health visits. These large databases contain healthcare information on the majority of the elderly population in the United States. Medical procedures and diagnoses are recorded in standard coding conventions. These data are a good source for obtaining denominator and descriptive information for the use of certain devices, and cost and use data for the elderly population. However, there is no information on younger age groups, and detailed claims data are not available on managed care plan members.

4. Harvard Pilgrim Health Care

This is a fully automated medical record system with computerized pharmacy records. This HMO has 300,000 active members with healthcare records maintained since 1990. The enrollment size limits study of rare events, but information on use for some devices is good because brand and model information is available.

5. Managed Care Data Sources

This is a large, relatively inexpensive database, with easy access to medical records and access to hospital discharge and diagnoses information. There is incomplete information on confounders and one may not be able to generalize the results.

6. National Mortality Followback Survey

This includes data from a population-based survey of individuals aged 15 years or older who died in the U.S. during 1993. The sample used for the survey was 22,957 death certificates. The survey sample was selected by age, race, and gender, with some oversampling of certain groups. Included are a wide range of decedent characteristics, such as occupation, income, activities of daily living, associated medical devices, and alcohol consumption.

7. National Health and Nutrition Examination Survey

This survey of the health of the general population includes results of physical examination and diagnostic tests. The data useful to the Center for Devices is restricted to commonly used devices, but can be used to make national estimates.

APPENDIX D

Enhanced Research in Epidemiology

To improve methodologies for evaluation of computerized medical product safety surveillance data, FDA's centers have an opportunity to adapt proactive screening methods from other disciplines and settings (e.g., biostatistics, quality improvement). These methods may allow more extensive and efficient monitoring of postmarketing adverse event reports and other data. Such techniques as exploratory data analysis, control charts, and time series modeling contrasts with the reactive mode, in which FDA responds to an inquiry or other external action by evaluating adverse event reports.

Analysis of Premarketing Data

Each center is striving to improve the analysis of premarketing safety data to focus the efforts of postmarketing reviewers. This knowledge transfer is becoming more streamlined and efficient. Residual safety concerns are identified (e.g., elevated liver enzymes) so that postmarketing ADR reports with similar syndromes (e.g., liver failure) will receive greater scrutiny. In this way, the complete safety profile of the product can be based on both pre- and postmarketing safety data.

Information Systems

The growth and development of computerized information systems supporting medical practice in well-defined populations will play an important role in drug safety surveillance as pharmacoepidemiological research systems transcend the limitations of passive surveillance from spontaneously submitted case reports. They come close to achieving active surveillance and greatly enhance the capability of objective epidemiological analyses. One new area may be the generation of signals from these large linked databases, which has been controversial and has had very limited success. Recent developments suggest promise for proactive systematic signal searching, although its complete role in generating an early alert has not been delineated. Systems featuring consistent ascertainment of outcome events may also be valuable for screening well-defined populations to evaluate moderate risks for relatively common or long-latency diseases impossible to distinguish from background noise in the spontaneous surveillance systems.

Another role for large information systems in pharmacoepidemiology is to help understand reporting rates by developing *background* incidence rates for diseases or syndromes in a population. For the relatively modest cost of conducting additional detailed chart reviews,

product-related studies of a given syndrome could be extended to the descriptive epidemiology of the condition in the general population.

APPENDIX E

Examples of Risk Assessment

Medication Error Interventions

1. Mivacron Deaths

Issue: On July 8, 1993, Mivacron (mivacurium chloride), an intravenous short-acting, nondepolarizing skeletal muscle relaxant, was inadvertently given to four patients, instead of a metronidazole injection. This incident resulted in one death and three injuries.

Investigation by the Agency revealed both products were packaged similarly in a foil overwrap manufactured by Abbott. Both product packages had the same dimensions and both were overwrapped with an aluminum laminated sleeve with a window for the label. The sleeve design allowed the product inside to slide down, thus obscuring the label. Eleven different products were being manufactured with this foil overwrap.

Burroughs Wellcome, the distributor of Mivacron, had begun to receive reports of potential problems and had issued a Stat-Gram on June 4, 1993. The Stat-Gram was issued to hospital pharmacists, bringing to their attention the possibility of a mix-up of the muscle relaxant Mivacron with other products, and informing them of new labeling for the product. In addition, the firm provided stickers to apply on the current stock of Mivacron in the hospitals.

Also contributing to the error were procedures at the hospital pharmacy that included the placement of Mivacron in the IV bin for metronidazole, placement of the prescription label over the window on the outside foil, failure to place the stickers on the Mivacron packages, and failure to check the accuracy of the product supplied at the time of administration.

FDA Action: Realizing that the packaging of the products contributed to the error, the Agency began discussions with Abbott concerning remedial actions that could be undertaken to prevent future mix-ups. After several conferences with Abbott, the parties agreed on two actions.

Outcome: The first outcome was an alert to all hospital pharmacy directors concerning the potential for mix-ups between Mivacron and other similarly packaged products, listing all 11 products. The second and more important outcome was an agreement to have complete labeling on the foil outer wrap. In addition, the back of each IV bag would be labeled with the drug name and strength.

2. Hetastarch Deaths

Issue: Hetastarch, a plasma volume expander, is often used in patients in emergency situations to restore lost volume of fluids. It was packaged in a plastic IV container, and users often applied manual pressure on the bag to force the Hetastarch into a fluid-depleted patient. After the original approval of the product, the firm submitted a supplement to change the plastic IV container. The supplement was approved, but it was soon discovered that the new packaging configuration had approximately 50 mL of air that had not been present in the originally approved packaging. Several deaths occurred due to air embolus, when users applied manual pressure on the new IV container of Hetastarch and inadvertently introduced air embolus.

FDA Action: FDA began discussions with the manufacturer to ascertain what remedial actions might be undertaken to minimize this problem in the future. After several discussions between the manufacturer and the FDA, three items were agreed to.

Outcome: First, a Dear Healthcare Professional Letter was issued by the company, alerting healthcare practitioners of the problem and potential for air embolus. Second, the manufacturing process was modified to reduce the amount of air in the IV package. Third, the labeling of the product was changed to alert the user to withdraw all air from the bag prior to manual pressure infusion.

APPENDIX F

Examples of Risk Confrontation

Collaboration/Partnerships with Stakeholders

1. Thalidomide

Issue: Although beneficial in the treatment of erythema nodosum leprosum (ENL), FDA had serious concerns about the risks related to thalidomide's use in women of childbearing age or pregnant women.

FDA Action: FDA invoked unprecedented regulatory controls over the marketing of thalidomide in the U.S. During the approval process, FDA's Dermatologic and Ophthalmic Drugs Advisory Committee listened to presentations from FDA, the product sponsor, and interested members of the public regarding the risk and benefits of thalidomide use. Public participants included representatives from the Canadian Thalidomide Victims Association. Following the presentations, the Committee voted that thalidomide was effective for the treatment of cutaneous ENL lesions.

Subsequently, on September 9-10, 1997, FDA, NIH, and CDC cosponsored an open public scientific workshop to further discuss the potential benefits and risks of thalidomide, including the medical, scientific, legal, ethical, and other policy issues related to research and treatment. There was extensive discussion of the proposal of Celgene Corporation (the product sponsor) for a fetal exposure prevention program.

FDA approved thalidomide for the treatment of ENL on July 16, 1998, along with regulatory controls over marketing the product in the U.S. To ensure safe use of the drug, Celgene developed a comprehensive program for patients, physicians, and pharmacists, in cooperation with experts in public health and women's health. The System for Thalidomide Education and Prescribing Safety (STEPS) oversight program includes limiting authorized prescribers and pharmacies, providing extensive patient education about the risks associated with thalidomide, and providing a 100 percent patient registry. This program is designed to help ensure a zero tolerance policy for thalidomide exposure during pregnancy.

FDA's efforts to inform the public about the approval of thalidomide included telephone conferences with members of the consumer, patient, and healthcare communities, extensive press interviews, and background briefings. The Center for Drugs created a thalidomide Internet page (www.fda.gov/cder/news/thalidomide.htm) to present consumer and patient information, thalidomide advisory committee and workshop transcripts, the approved labeling text, and the medical review on which the decision to approve this drug was based. This thalidomide page

includes selected links to other websites containing thalidomide information.

Outcome: Thalidomide was approved by FDA with a risk management program that limits authorized prescribers and pharmacies, provides extensive patient education about the risks associated with thalidomide, and provides a 100 percent patient registry. This program is designed to help ensure a zero tolerance policy for thalidomide exposure during pregnancy. As of April 1999, FDA has received no reports of thalidomide exposure during pregnancy.

2. Tamoxifen

Issue: In 1998, FDA received the first application (supplemental new drug application) to market a drug for a cancer prevention indication. Interim results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial had shown that tamoxifen reduced breast cancer incidence by almost one half. However, two other studies reported no significant difference in the number of breast cancer cases between women taking tamoxifen and women given placebo. In addition, questions were raised about tamoxifen's treatment benefits versus its risks of serious side effects, including endometrial cancer, deep vein thrombosis, stroke, cataract formation, and pulmonary embolism. Some of the events reported were fatal. Furthermore, the study did not demonstrate a reduction in overall or breast cancer specific mortality with tamoxifen treatment.

Action: FDA convened the September 1998 Oncologic Drugs Advisory Committee (ODAC) meeting to discuss the results of the National Cancer Institute (NCI) sponsored NSABP Breast Cancer Prevention Trial (BCPT) and two *Lancet* articles published in July 1998, following Zeneca's supplemental new drug application. The BCPT included over 13,000 patients and was halted 14 months early when interim results showed that tamoxifen reduced breast cancer incidence by almost one half. However, the *Lancet* articles reported that European scientists found no significant difference in the number of breast cancer cases between women taking tamoxifen and women given a placebo.

Data from the studies were presented at the ODAC meeting and discussed in great detail. FDA invited Trevor Powles, the author of one of the European trials, to present his trial and comment on the difference in results. The meeting was well covered by the media and the public comment session provided a forum for comments from consumer, women's health, and breast cancer patient advocates. Many committee members and public speakers raised concerns about Zeneca's proposed tamoxifen indication for prevention of breast cancer in women at high risk, in that treatment with tamoxifen did not completely eliminate breast cancer risk and that its longer-term effects were not known. Also, ODAC recommended that NSABP perform additional studies on banked specimens that might identify women at particularly high risk of certain adverse events.

Outcome: On October 29, 1998, FDA approved tamoxifen for reducing the incidence of breast cancer in women at high risk for developing the disease. Zeneca was asked to provide an educational program for physicians and patients, including information about the drug's potential benefits and risks. The approval included a professional and patient information brochure and a

breast cancer risk assessment tool developed by NCI.

8. Latex Allergy

Issue: Cases of sudden death associated with the use of barium enema kits were reported to the FDA in 1989 and 1990. In some instances, the reported incidents occurred prior to the introduction of the barium solution.

FDA Action: Based on these reports, FDA postmarketing clinical area experts initiated an investigation and follow-up that directed firm inspections and a comprehensive review of the scientific and clinical literature. This review revealed the potential for serious allergic or anaphylactic reactions to devices containing natural rubber latex.

As a result of FDA's initial postmarketing investigation of these reports, one manufacturer of natural rubber latex cuffed enema tips voluntarily agreed to send a Medical Alert to approximately 10,000 practicing radiologists, alerting them to the possibility of allergic reactions to latex-containing enema tips. The Alert advised healthcare professionals to minimize the use of tips with retention cuffs and recommended the use of noncuffed tips whenever possible. Physicians were also urged, for the first time, to screen patients for latex allergy history prior to procedures. Based on additional health hazard evaluations of inspection findings, FDA determined that the problems associated with the firm's latex cuffed enema tips presented a high risk of serious adverse health consequences. Thus, FDA recommended that the firm's Medical Alert be expanded to include more health professionals and organizations. As a result, the firm expanded their clinical alert and initiated a nationwide recall of all their latex cuffed enema tip products.

FDA's postmarketing activities have continued to be a catalyst for both national and international clinical education efforts, scientific and clinical research, and voluntary standards activities on natural rubber latex allergy. Notable postmarketing activities are listed below.

- FDA issued a 1991 medical alert entitled "Allergic Reactions to Latex-Containing Medical Devices." This indicated that FDA considered the problem to be generic and not limited to barium enema tips. The alert suggested ways to identify and protect allergic individuals in clinical settings. This alert was provided to approximately 1,000 radiological and medical organizations and was published in the July 1991 *FDA Medical Bulletin*.

- The Center for Devices sent a letter to all manufacturers of latex-containing devices that discussed how to manufacture latex products to minimize the possibility that latex contaminants are either a source of, or a contributing factor to, adverse reactions.

- In 1992, the Center for Devices sponsored the first international forum for addressing natural rubber latex allergy. The conference was entitled International Latex Conference: Sensitivity to Latex in Medical Devices, and was cosponsored by CDC and the National Institute of Allergy and Infectious Diseases (NIAID).

- The Center for Devices sponsored a March 1994 workshop entitled Contact Sensitivity to Latex. Recommendations from expert participants were used as a basis for developing a Center for Devices guidance document entitled Testing for Skin Sensitization to Chemicals in Natural Rubber Products.

- FDA devoted the Spring 1997 edition of FDA's *User Facility Reporting Bulletin* entirely to natural rubber latex allergy issues. This bulletin was sent to over 70,000 healthcare professionals in hospitals, nursing homes, other user facilities, and healthcare professional organizations.

- FDA proposed regulations to help healthcare professionals and consumers identify medical devices that contained natural rubber latex to facilitate the ability of clinicians to provide latex-free products for individuals with diagnosed latex sensitivity. "Natural Rubber-Containing Medical Devices; User Labeling," was published as a final rule in the Federal Register (62 FR 51021, September 30, 1997).

- The Center for Devices Medical Glove Working Group released the Medical Glove Powder Report in September 1997. This document is available as a resource to regulated industry and consumers.

- The Center for Devices and its Office of Surveillance and Biometrics (OSB), worked with the Office of Health Affairs (OHA) and the Food and Drug Law Institute, initiating and leading a precedent-setting postmarketing initiative to develop and fund a live educational teleconference in recognition of the need for Federal agencies to provide their constituencies with current, consistent scientific and regulatory information on natural rubber latex allergy. The collaboration involved seven Federal agencies, seven major U.S. health professional and industry organizations, the Canadian Royal College of Physicians and Surgeons, and Health Canada. The goal of this consortium was to create an educational resource that would provide important baseline information to healthcare professionals and others concerned with latex allergy, and that could serve as a resource for similar collaborations in the future.

Outcome: This benchmark collaboration resulted in the broadcast of a live educational teleconference entitled Natural Rubber Latex Allergy: Recognition, Treatment, and Prevention, May 5, 1998. Due to the power of the combined marketing efforts of the cosponsoring groups and medical device manufacturers, the satellite teleconference reached the largest live audience of multidisciplinary healthcare professionals and others ever assembled. FDA alone mailed out over 130,000 teleconference brochures to various healthcare professionals.
The teleconference continues to serve as a consumer and industry resource due to its continued availability on videotape, CD-ROM, and as an Internet webcast. Each year *Teleconference Magazine* and TeleCon honor the most outstanding achievements in teleconferencing, business television, and distance learning. Award recipients are judged on their immediate or potential future impact on interactive multimedia communications, and the product must provide a new or unique solution to ensure seamless high quality transport and use of video, voice and/or data.

These awards are often referred to as the Academy Awards of Teleconferencing. In recognition of the innovative use of multimedia formats for presenting the clinical educational material, the latex allergy teleconference was awarded second place for *Best User Application* in the Interactive Multimedia Communications category.

4. Regulation for the Waiver of Informed Consent in Clinical Trials

Issue: FDA wanted information and input from Federal, private, and public sectors regarding the development of the regulation for the Waiver of Informed Consent in Clinical Trials involving emergency research.

FDA Action: The Office of Health Affairs, in collaboration with the Office for Protection from Research Risks at NIH, held open public conferences and workshops during the development of the rule and after the rule's implementation. These conferences provided an opportunity for interested parties to raise concerns about the rule's potential impact and for FDA to learn about details to assist in implementation following the rule's publication.

Outcome: The information gained from meetings with the relevant parties affected was used to publish the regulation.

5. The Center for Devices STAMP Program with Cerebrospinal Fluid (CSF) Shunt

Issue: Procedures are needed to engage the healthcare community to discuss the risks associated with medical products and motivate the manufacturing community to improve the risk-benefit profile of the highlighted products.

FDA Action: An example of FDA engaging the healthcare community in the goal of minimizing risk and improving technology in our regulated products is the Center for Devices' new Systematic Technology Assessment of Medical Products (STAMP) program. In this program, the Center identifies products with potentially significant problems that also offer significant clinical benefit. STAMP provides a forum to discuss products in the anticipation that this will motivate the healthcare and manufacturing community to improve the products' risk-benefit profiles. Information for this forum is provided by journal articles, public workshops, conferences, and FDA advisory panels. A recent example is CSF shunts.

Neurological CSF shunts have served a purpose in the overall armamentarium for treating hydrocephalus for over 40 years, but literature and adverse event reporting indicated continuing problems. Standards provide some guidance for mechanical testing but this alone has not been effective in predicting the clinical performance of these devices. The Center for Devices believed that holding a conference on the subject of shunt technology would provide an opportunity to examine the current state of the technology and explore different approaches to improve patient outcomes. Since there were a variety of stakeholders interested in this subject and the current research seemed fragmented, a conference format was selected that allowed the Center for Devices to use a multidisciplinary approach to tackle the issues. The conference was held on

Friday, January 8, 1999, at the National Naval Medical Center (NNMC). NNMC was chosen in an effort to expand Agency contact with the military medical community and establish further collaboration.

The Center for Devices contacted all of the known stakeholders for input and decided on four session topics:

1. Shunt Technology Perspectives. Stakeholder representatives (from the Hydrocephalus Association, the American Association of Neuroscience Nurses, industry, and a neurosurgeon) spoke about their perspectives on the issues.

2. Hydrocephalus and Assessment of Shunt Function. Scientific talks on the pathophysiology and methods of evaluating shunt performance were presented.

3. Challenges of Infection and New Perspectives. Issues of shunt-centered infections and the emergence of antimicrobial resistance were discussed.

4. Clinical Outcomes and Methods of Surveillance. Strategies to improve clinical outcomes and the performance of CSF shunts were presented.

Following the four sessions, a panel discussion was held to establish priorities. The panel consisted of FDA and NIH representatives, several notable neurosurgeons, and a representative of a patient group.

Outcome: The Center for Devices is now in the process of reviewing the material presented during the conference and plans to submit a summary article for publication in several journals so that what was shared on January 8, 1999, can reach a larger audience. The Center for Devices will propose some recommendations that will include further involvement of stakeholders and perhaps publishing an update of action items completed or in progress. Some proposed recommendations include developing better patient labeling that would include information on a patient's specific implant, continued work on standards development with new contacts and players to be involved, and a collaborative effort to collect data on CSF shunts using the on-line outcomes database of the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS).

6. Blood Products and CJD

Issue: While there are no recorded cases of Creutzfeldt-Jakob Disease (CJD) transmission in humans through blood, there is a theoretical possibility for transmission from donors with or at risk for CJD. Ensuring the safety of America's blood supply is a high priority for FDA. Thus, FDA needed to take aggressive actions to mitigate the potential risk of CJD transmission and decide how best to protect the public health, having only incomplete or emerging scientific knowledge.

FDA Action: As clinical and epidemiological knowledge of CJD has increased, FDA has responded aggressively by reviewing and modifying its policy and communicating revised recommendations to the healthcare community. Throughout this process, FDA has worked closely with CDC and NIH, among others, in determining the most appropriate regulatory course of action. FDA has also had extensive discussions with all segments of the community involved, including medical professionals, academicians, industry representatives, and recipients of blood components and products.

FDA's involvement in addressing the possible impact of CJD on the Nation's blood supply began with the early awareness of possible transmission. In 1987, FDA issued a memorandum to all blood establishments, recommending that all persons who received human growth hormone (HGH) defer donating blood or plasma. For the period of 1983-1992, there were only four reported blood donors who had a confirmed diagnosis of CJD reported postdonation. Blood and plasma manufacturers initiated a voluntary withdrawal of in-date products that had been prepared for donation from the individuals with a confirmed diagnosis of CJD.

In 1993, FDA expanded its position and issued recommendations for more complete reporting of safety-related information from blood and plasma donors postdonation. In 1994 and early 1995, FDA began receiving additional reports of CJD-affected individuals who had donated blood and plasma. At FDA's request, the manufacturers placed in-date, licensed, retrievable derivatives of blood and plasma, as well as products used in further processing, into quarantine. Market withdrawals for CJD were discussed at the Blood Products Advisory Committee (BPAC) in 1994 and 1995; however, the committee was unable to reach consensus on all of the issues related to product disposition and recipient notification.

In an effort to further develop policy on CJD, FDA formed a Special Advisory Committee on CJD, later rechartered the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), to address outstanding issues and encourage additional public discussion and consideration. (The outcome of this meeting is presented below.) TSEAC also met to discuss recommendations for reentering deferred donors based on genetic testing and the disposition of plasma derivatives prepared from products collected from donors having a family member diagnosed with CJD. In 1996, FDA and the National Heart, Lung, and Blood Institute (NHLBI) sponsored a workshop on Design of Experimental Studies of Transmission of CJD, and FDA participated in a Canadian Consensus Conference (CJD — Decision Making in Times of Uncertainty) and a liaison meeting with the Pharmaceutical Research and Manufacturers of America (PhRMA) regarding transmissible spongiform encephalopathies (TSE). In addition, CJD policy was discussed at seven Public Health Service (PHS) conference calls attended by representatives of the Center for Biologics, CDC, NIH, and the Department of Defense.

Outcome: After considering recommendations from TSEAC and after extensive internal discussions, FDA issued an interim policy that broadened guidance on donor exclusion for CJD risk and called for withdrawal of implicated blood products. Provisions were made for release of affected products with special labeling, in case of a documented shortage. FDA and NIH also held a workshop on design of experimental studies on transmission of CJD.

FDA revised its recommendations for CJD in 1996 and again in 1998 to include retrieval, quarantine, destruction, and notification of consignees in the event that in-date products are manufactured from donors who developed new variant CJD. In its decision, FDA carefully considered the delicate balance of the need for the products and the risk of using the products. FDA made information concerning product recalls and market withdrawals widely available to interested and affected parties through voice information systems, fax-on-demand, automated e-mail, and the FDA Home Page. In addition, industry is implementing a registry that will allow for notification of individual product users. For the BPAC, the Center for Biologics routinely provides updates on CJD policy discussions and changes.

7. Abnormal Fat Redistribution

Issue: HIV/AIDS-related abnormal fat redistribution, or lipodystrophy, is a complex syndrome that occurs among patients receiving protease inhibitors and other antiretroviral agents. Further knowledge is needed to address this product risk.

FDA Action: To help coordinate efforts to define, track, and seek appropriate approaches to HIV/AIDS-related abnormal fat redistribution, FDA is working with the HIV/AIDS community and other government agencies to discuss the current situation and communicate about what steps need to be taken to address the problems. Because abnormal fat redistribution is a complex syndrome that crosses several medical subspecialties, extensive collaboration by government, and academic and pharmaceutical scientists will be required. FDA may be able to stimulate pharmaceutical sponsor interest in certain projects related to abnormal fat redistribution. FDA has requested additional information from sponsors regarding reports of abnormal fat redistribution among patients receiving protease inhibitors and proposed package insert revisions to include information on abnormal fat redistribution. All protease inhibitor package inserts have been or soon will be revised to include this information. FDA has also encouraged sponsors to investigate potential mechanisms for abnormal fat redistribution and to assess the frequency of this syndrome in ongoing and future trials. FDA has sent a follow-up letter to sponsors asking them to enumerate ongoing or planned research projects that may address issues relating to abnormal fat redistribution.

The Agency is working in a consultative capacity to the NIAID AIDS Clinical Trials Group and the Forum for Collaborative Research in HIV/AIDS to develop a case definition for this syndrome. Based on a workable case definition, FDA plans to ask pharmaceutical sponsors to monitor changes in body morphology in ongoing and future clinical trials of antiretroviral drugs. FDA is also working with the NIH working group on Metabolic Complications of Antiretroviral Therapies, which will include representatives from several NIH institutes and the Department of Veterans Affairs, to develop suggestions for research into potential mechanisms for this syndrome. FDA has a representative on this working group and will attempt to stimulate interest among pharmaceutical sponsors to collaborate with Government and academic scientists in suggested research projects.

Outcome: FDA has requested that protease inhibitor sponsors revise the product labeling to include risk information about abnormal fat redistribution and plan research to study the problem. FDA is continuing to work with the healthcare community and other agencies to gain further insight about how to manage this product risk.

8. Vaccine Safety

Issue: Nearly every child in the United States is immunized for vaccine preventable diseases, but unlike other pharmaceutical products, vaccines are given to mostly healthy children and infants. The irony of the success of the immunization programs, demonstrated by the near or record low levels of occurrence of most vaccine-preventable diseases, is that there is a loss of awareness about the severity of the diseases prevented by the vaccination program. This loss of disease awareness results in reduced tolerance for adverse reactions following vaccination and loss of parental confidence. Loss of parental confidence in the vaccination program may cause parents not to have their children vaccinated in accordance with recommendations, resulting in outbreaks of vaccine-preventable diseases with subsequent increases in morbidity and mortality.

FDA Actions: To limit the risks of vaccinations to healthy children, FDA collaborates with other Public Health Service (PHS) agencies and healthcare organizations to study or address issues of vaccine safety. For example, FDA participates in a variety of PHS cross-agency efforts on vaccine safety and has liaisons on other PHS advisory groups, such as the National Vaccine Advisory Committee, the Advisory Commission on Childhood Vaccines, and the Advisory Committee on Immunization Practices. FDA also has a liaison to the American Academy of Pediatrics' Committee on Infectious Diseases.

One cross-agency group in which FDA participates is the Interagency Vaccine Group (IAVG), coordinated by the PHS National Vaccine Program Office. IAVG analyzes extensive risk-benefit data in response to public concerns about safety and has played a major role in the development of the National Vaccine Plan, the Pandemic Influenza Plan, and the Vaccine Safety Action Plan.

In addition, FDA had representatives on the Task Force on Safer Childhood Vaccines that was established by the Secretary of HHS at the direction of Congress. This task force examined vaccine safety and made recommendations to the Secretary to ensure research and development of safer childhood vaccines and to improve such factors as licensing, manufacturing, labeling, and adverse reaction reporting for vaccines.

Outcome: Collaborative efforts have addressed and continue to address areas to ensure vaccine safety.

The Task Force on Safer Childhood Vaccines recently issued its final report with several recommendations for vaccine safety. One recommendation was to charge the IAVG with the ongoing responsibility of ensuring that appropriate vaccine safety activities are carried out. The group would monitor the vaccine safety activities of the various agencies and work to improve interagency communication.

The National Vaccine Program Office was charged by the Secretary with implementing the recommendations of the Task Force (i.e., to develop a vaccine safety action plan). The IAVG developed the Vaccine Safety Action Plan, which details a variety of actions that need to be initiated or continued to ensure vaccine safety.

9. The Center for Devices and Other Healthcare Organizations

Issue: Risks associated with the use of some medical device products may occur following market approval.

FDA Action: The Center for Devices interacts with other healthcare organizations to evaluate or perform specific investigations of device problems from existing databases and registries. Examples include the National Center for Health Statistics National Mortality Follow Up Survey, the Medicare Database from HCFA, Harvard Pilgrim Health Plan, and the NACI Registry for Coronary Implants. The Center for Devices also evaluates patterns of failures and injuries, using open workshops, focus groups, and questionnaires.

Outcome: These interactions have resulted in the publication of brochures, checklists (used by professionals in their everyday practice), guidance to industry for the development of safer products, guidance to users on injury avoidance practices, manuals to assist the industry in its risk communication about product labeling and interactions with its customers, and a series of video tapes that provide instruction for a variety of medical devices.

APPENDIX G

Risk Intervention Examples

A. Restrictions on Product Use

1. Thalidomide (See description in Appendix F.)

2. The Center for Devices Postmarketing Study Requirements

Issue: Premarket testing does not address all device-related concerns about a product.

FDA Action: FDA can require a manufacturer to conduct postmarketing surveillance as a condition of approval for a product brought through the premarketing approval (PMA) process or as part of FDA's authority to require postmarketing studies for high risk products under section 522 of the FD&C Act. The Modernization Act changed the scope of section 522. To implement these new provisions, the Center for Devices issued a guidance that outlines criteria the Agency intends to use routinely to implement postmarketing surveillance (*Guidance on Criteria and Approaches for Postmarket Surveillance*, issued November 2, 1998).

Outcome: The guidance provides general principles that will guide FDA's decisions concerning postmarketing surveillance. It identifies products in categories and describes how the needs for postmarketing surveillance will be assessed. These products may have been approved through either the PMA process or section 510(k) of the FD&C Act. The products may have been on the market for some time or may be new to the market.

In addition, the Center for Devices provides written notice of the general and specific postmarketing requirements to each holder of a PMA at the time of approval. The Center for Devices provides descriptive information about the product, the training required for professionals prior to the use of some products, and manuals that give detailed instructions for the setup, use, and maintenance of the equipment. For many medical devices, additional labeling intended for the patient, usually an information booklet, is also required at the time of market entry.

3. Proleukin (Aldeskleukin)

Issue: Proleukin is an example of a product where FDA identified a risk associated with the product and restricted its use through information in the product labeling.

FDA Action: FDA identified that there were risks of heart attack and sudden death associated with Proleukin early in IND development by reviewing the development plans of multiple IL-2 products submitted by sponsors. FDA was able to attribute the small number of heart attacks and sudden deaths to the product and not to other factors.

Outcome: FDA instituted procedures in the clinical trials to ensure that patients were given the product in a controlled environment (i.e., hospital setting). On approval, the Center for Biologics included boxed-warning information in the labeling, specifying product administration conditions and restricting the product use to patients with normal cardiac and pulmonary function.

4. Measles, Mumps, and Rubella Vaccine (MMR)

Issue: As a part of the monthly review of reports from the Vaccine Adverse Events Reporting System (VAERS), FDA noted that thrombocytopenia following immunization with measles-containing vaccines was more severe than was previously perceived. Approximately 40 percent of reports of postimmunization thrombocytopenia described cases with platelet counts 20,000, a level that has been associated with spontaneous life-threatening hemorrhage. In reviewing all reported cases of post-MMR thrombocytopenia in VAERS, FDA found one case of thrombocytopenia that resulted from positive rechallenge with MMR vaccine. FDA also found two deaths that occurred in children with postimmunization thrombocytopenia; however, these two children had complicated medical histories, so a direct causal relationship with vaccination could not be made.

FDA Action: FDA discussed these findings and searched the literature for similar reports. The search showed that investigators in Finland had reported that 30 percent of children with thrombocytopenia after MMR immunization had detectable anti-IIbIIIa platelet antibodies. Following these reports, FDA's Laboratory of Pediatric and Respiratory Diseases initiated a research study to identify the vaccine antigens that might be responsible for inducing antiplatelet antibodies. These studies showed that (1) vitronectin receptor proteins derived from the chick embryo fibroblast cells (CEFs) used as the substrate for production of measles and mumps vaccine cross-react with anti-IIbIIIa platelet antibodies; (2) in mice, immunization with measles vaccine or with CEFs induces anti-IIbIIIa antibodies; (3) antibodies to measles matrix protein also cross-react with platelet protein IIIa; and (4) following immunization with measles vaccine 0.5-1 percent of children develop antibodies that react with human IIbIIIa, indicating that they may be at risk for episodes of immune thrombocytopenia when reexposed to any vaccine that contains cross-reacting antigens.

Outcome: Based on the review of the VAERS data and the literature, labeling for measles-containing vaccines was revised to provide adequate information to warn and inform healthcare providers about the use of measles vaccine in children with thrombocytopenia or with a history of thrombocytopenia following previous doses of MMR. The Center for Biologics research suggested a mechanism as to why there might be an association with thrombocytopenia and MMR vaccines in some individuals.

B. Center for Biologics and Center for Drugs Phase-4 Commitments

1. Herceptin (Trastuzmab)

Issue: Herceptin is a monoclonal antibody approved for the treatment of patients with metastatic breast cancer whose tumors express the HER2 protein and who have received one or more chemotherapy regimens. Clinical adverse event reports showed symptomology of cardiac toxicity.

FDA Action: FDA requested that the Data Safety Monitoring Board (DSMB) look at cardiac toxicity during an interim data analysis. Based on the interim analysis, FDA worked with the manufacturer to revise consent forms and reinstitute cardiac monitoring. Further data analysis showed that patients who were treated with Herceptin in combination with anathracyclines and cyclophosphamides had a particularly high incidence of cardiac dysfunction.

Outcome: When approved for market, the Center for Biologics required boxed-warning information in the product labeling for physicians using the product to treat patients who also have cardiomyopathy. The Center for Biologics also required that patients with early signs of Herceptin-induced cardiotoxicity be evaluated to weigh the risks and benefits of continuing therapy with Herceptin. The manufacturer committed to a postmarketing study in patients using the product.

2. Celebrex (celecoxib capsules)

Issue: Celebrex, a new COX-2 selective nonsteriodal anti-inflammatory drug (NSAID), was approved for use in the treatment of osteoarthritis and rheumatoid arthritis. Studies used for the basis of approval showed that patients taking Celebrex had a substantially lower risk of ulcers detected by endoscopy over the study period of 12 to 24 weeks, as compared to patients who took other NSAIDS. However, FDA believed that the limited data available on gastrointestinal outcomes were not sufficient to support a product claim that Celebrex was safer than other NSAIDs regarding serious GI effects. Such a claim would need additional studies in many thousands of patients to demonstrate that Celebrex causes fewer clinically important GI complications.

FDA Action: On approval, FDA included a slightly modified standard warning in Celebrex's approved product labeling for doctors and patients about the risk associated with NSAIDS, including risks of GI ulceration, bleeding, and perforation, and requested further study of the GI and renal effects.

Outcome: The product sponsor committed to studying the GI effects further using protocols agreed to by FDA. If additional information relating to the safety or effectiveness of the drug product becomes available, substantial revision of the product labeling may be required.

C. Market Withdrawals/Recalls

1. Blood products (See previous blood product CJD example.)

2. Drug Withdrawals

    a. Posicor (mibefradil)

Issue: On approval of the product in August 1997, FDA described enzyme-inhibiting properties in Posicor's approved labeling and listed three drugs that could accumulate to dangerous levels if coadministered with Posicor (a calcium-channel blocker). FDA strengthened the labeling in December 1997 after learning of several cases in which patients suffered serious adverse reactions after taking Posicor with one or more of other drugs. FDA included more drugs in the labeling that should not be administered with the product and issued a public warning about the problem. The company also issued a Dear Healthcare Professional letter alerting healthcare professionals of the drug interaction problems.

FDA and the company continued to learn of adverse reactions related to coadministration of Posicor with other drugs. More than 25 drugs were known to be potentially dangerous if used with Posicor — a number and diversity of drugs that cannot be practically addressed by standard labeling warnings.

FDA Action: Due to the complexity of the prescribing information needed for Posicor and the seriousness of the side effects, FDA and the company agreed that it would be difficult to administer Posicor safely. In addition, Posicor had not been shown to offer special benefits, and its problems were viewed as unreasonable risks to consumers.

Outcome: The company voluntarily withdrew Posicor from the market as a result of new information about potentially harmful interactions with other drugs.

    b. Duract

Issue: FDA and the company received postmarketing reports of severe hepatic failure associated with the use of the nonsteroidal anti-inflammatory analgesic Duract, resulting in four deaths and eight liver transplants. All but one of the cases involved the use of Duract for longer than 10 days — the maximum recommended duration of treatment.

FDA Action: In response to the reports, FDA and the company strengthened the warnings in Duract's labeling with a special black-box warning and the company issued a Dear Healthcare Professional letter. Despite these efforts, the Agency and the company continued to receive reports of severe injuries and death with long-term use of Duract.

Given the availability of other therapies, FDA and the company concluded that it would not be practical to implement the restrictions necessary to ensure the safe use (less than 10 days) of

Duract and that the drug should be withdrawn from the market.

Outcome: Duract was withdrawn from the market.

c. Seldane

Issue: Seldane (terfenadine) and Seldane-D have been associated with rare but serious heart problems when taken with certain other drugs, including certain antibiotics and antifungals.

FDA Action: Due to the serious drug interaction, FDA proposed removing all terfenadine products from the marketplace because of the approval of a safer alternative drug, Allegra (fexofenadine), in January 1997. FDA also advised patients taking Seldane, Seldane-D, and generic terfenadine products to talk to their healthcare providers about switching to alternative medications.

Outcome: Following the approval of Allegra-D, the manufacturers of Seldane, Seldane D, and generic terfenadine discontinued U.S. distribution and marketing of the products. FDA has completed administrative procedures to finalize the permanent withdrawal of all terfenadine-containing products from the U.S. market.

3. Device Withdrawals

Issue: Medline Industries, Inc., marketed three basic versions of an enteral feeding pump. These pumps had a number of design defects apparently caused by an initial flawed design and/or lack of validation and the inability to comply with the GMPs.

FDA Action: The Center for Devices issued an order for recall and required Medline Industries, Inc., to stop distributing all Medline/Dynacor Dynafeed Enteral Feeding Pumps, to notify health professionals and device user facilities to stop using the device immediately, and to recall the products on the market.

Outcome: The defective devices were recalled from the market.

D. Interventions by Enforcement Activities

HIV Home Test Kits

Issue: In 1998 the Office of Special Health Issues was notified by constituents that HIV home test kits were being advertised and sold over the Internet. Results from these kits could be obtained immediately and in the privacy of the home. No such kits had ever been approved by FDA. The Office of Compliance and Biologics Quality at the Center for Biologics had also received complaints about the kits.

Home HIV test kits are medical devices within the definition of section 201(h) of the FD&C Act

and are regulated by the Center for Biologics as Class III devices under the current Intercenter Agreement between the Center for Devices and the Center for Biologics.

Because the HIV home test kits being sold over the Internet were unapproved, there was no assurance that the test kits were manufactured under good manufacturing practices, that the kits had been tested properly, or that the results obtained by the persons testing themselves would be accurate. This could have presented a serious hazard to the public health, including possible HIV transmission to partners and delayed access to medical care due to false negative test results. The home HIV test kits sold over the Internet did not have capabilities for confirmatory testing. Furthermore, there was no provision for counseling and referral for confirmatory testing or medical and social support services in the area where the patient lived.

FDA Action: The Office of Special Health Issues (OSHI) and the Center for Biologics worked closely to find ways that the Internet promotions could be halted. A Question and Answer (Q&A) document was developed and posted on several of the Agency's web pages. A directed inspection of the firms took place and the Center for Biologics initiated several enforcement actions, including criminal prosecution and seizures of the products. The Federal Trade Commission (FTC) also joined with FDA to help stop the illegal sale of the HIV home test kits on the Internet.

Outcome: Websites of this type have been greatly reduced because of intra- and interagency cooperation. FTC continues to sponsor *Internet surf days* dedicated to looking for sale of fraudulent products on the Internet. With the Center for Biologics' cooperation, notices are sent to the websites notifying them of the violation and requesting that the site be removed.

APPENDIX H

Risk Communication Examples

A. FDA-Approved Patient Labeling

Issue: Consumer-friendly written risk information is not consistently available to patients for drug and biological products that pose a serious and significant public health concern.

FDA Action: In December 1998 a new regulation was made final requiring FDA-approved patient labeling (*Medication Guides*) for drug and biological products that pose a serious and significant public health concern. This rule is expected to be invoked for a relatively small number of products (on average, between five and ten annually).

The drugs that require patient information will be identified using one or more of the following criteria:

- Patient labeling could help prevent serious adverse events.

- Patients need to know of serious risks (relative to benefits) associated with a drug that might affect their decision to use or continue using the product.

- The drug is important to health, and patient compliance with directions for use is critical to the drug's effectiveness.

An action plan for the provision of useful prescription drug information was developed by the private sector and accepted by the Secretary of Health and Human Services in January 1997. This plan provides guidelines to encourage the development of written prescription medication information that is useful to consumers. Useful information is defined, in this context, as being sufficiently comprehensive and communicated in such a way that consumers can make informed decisions about how to receive the most benefit from medicines and protect themselves from harm. The plan provides criteria to judge this useful information in meeting the Agency's goal:

- By the year 2000, at least 75 percent of people receiving new prescriptions will receive useful written information.

- By the year 2006, 95 percent of patients who receive new prescription drugs will receive useful written information.

Outcome: FDA will require FDA-approved patient labeling for a small number of drug and biological products that pose a serious and significant public health concern. The private sector continues to develop useful patient prescription drug information in an effort to meet the goals in the action plan.

B. Outreach Programs

1. Specific Communication Programs

a. Take Time To Care Program

Issue: Women need to be more aware of safe medication use.

FDA Action: The FDA Office of Women's Health (OWH) created a national public awareness campaign called *Women's Health: Take Time to Care* (TTTC), *Use Medicines Wisely*, a program specifically designed to educate the general public about minimizing the risks associated with medication use. Working with the Office of Health Affairs (OHA), OWH will formally partner with the National Association of Chain Drug Stores (NACDS) and the program will be led by major health and service-related organizations at the grassroots level. OWH and NACDS are seeking the participation of drug stores, hospitals, HMOs, insurance companies, other Federal agencies, state and local governments, health centers, professional associations, and libraries to distribute the materials and discuss the messages.

The public will also be reached through the media on television and radio talk shows, newspaper, magazine, and newsletter coverage. Through the distribution sites, events, and media coverage, OWH and NACDS expect to reach tens of millions of Americans about safe medication use with the messages: Read the Label, Avoid Problems, Ask Questions, and Keep a Record.

Outcome: The TTTC program makes women, who are the principal users of medications[1] and who often administer them for family members, more aware of safe medication use. The program will include materials and interactive events led by pharmacists and other health professionals. In 1997, an OWH TTTC pilot program was tested in two cities: Hartford, Connecticut and Chicago, Illinois. Because the pilot programs were an overwhelming success, in 1998, OWH, in conjunction with FDA's field staff, took the program to fifteen cities, thirteen rural counties and a few Indian reservations. In 1999, OWH is planning to reach millions of women with the *Use Medicines Wisely* message. Activities will culminate with a major national blitz during the month of October 1999.

b. Public Health Advisories

i. Protease Inhibitors and Hyperglycemia

[1] The latest edition of the National Ambulatory Medical Care Survey (1995) reported that there were 4.25 prescriptions per year written for women and 2.79 prescriptions per year written for men (average of all age groups).

Issue: In the spring of 1997, reports had surfaced of hyperglycemia, worsening glucose control, and diabetes mellitus occurring with the use of HIV protease inhibitors.

FDA Action: In response to these initial reports, members from the Division of Anti-Viral Drug Products (DAVDP), OSHI, and the Division of Pharmacovigilance and Epidemiology evaluated and acted on what appeared to be a drug class adverse event for the HIV protease inhibitors. Because this adverse event involved four drugs marketed by four different pharmaceutical companies, skillful collaboration and negotiation were required to reach consensus on revisions to product labeling and the issuance of a product advisory.

Due to the unique situation of trying to issue simultaneous Dear Healthcare Professional Letters from four pharmaceutical sponsors, the group explored various options for the most rapid and efficient mechanism to disseminate this safety information. They concluded that the information could best be disseminated through an FDA Public Health Advisory. Because this is not the typical route of disseminating postmarketing safety information in the Center for Drugs, the group needed to ascertain how to ensure a timely and comprehensive distribution of the information, sources for funding the dissemination (printing, mailing) of this health advisory, and regulatory requirements.

Outcome: Within a month, the group completed the task of evaluating sentinel reports, analyzing the database, forming conclusions, and disseminating information. This information was shared with healthcare professionals in the United States, the HIV-infected patient community, and regulatory agencies throughout the world, including Japan, Canada, the U.K., and France.

The Division of Pharmacovigilance and Epidemiology, Reports Evaluation Branch, completed a search of reports submitted to the Spontaneous Reporting System (SRS). This evaluation showed that there were approximately 80 cases of hyperglycemia/diabetes mellitus occurring after the use of any one of the four marketed protease inhibitors.

The Division of Anti-Viral Drug Products coordinated and drafted a public health warning letter to be distributed to healthcare professionals and other regulatory agencies. Members of DAVDP, OSHI, and the Division of Pharmacovigilance and Epidemiology also participated in various community and healthcare professional teleconferences and addressed concerns and questions relating to this drug class safety issue.

OSHI identified mechanisms used by other Agency components to communicate risk information, evaluated options for the most expeditious and cost-effective means to distribute the information, completed a targeted mailing to 13,000 health professionals, and disseminated important safety information to other government agencies and the HIV/AIDS patient community.

ii. Low Molecular Weight Heparins/Heparinoids

Issue: On December 15, 1997, the Center for Drugs released a Public Health Advisory (PHA) on the reports of epidural or spinal hematomas with the concurrent use of low molecular weight

heparins and/or heparinoids and spinal/epidural anesthesia or spinal puncture. During the next few months, the Center for Drugs and MEDWATCH received a high volume of phone calls from the clinical community (predominantly anesthesiologists, obstetrician/gynecologists, and orthopedic surgeons) regarding the PHA.

FDA Action: Given the concerns expressed by these health professionals, MEDWATCH and the Center for Drugs established a working group composed of representatives from the Division of Gastro-Intestinal and Coagulation Drug Products, the Division of Anesthetic, Critical Care, and Addiction Drug Products, the Office of Training and Communication, Division of Pharmacovigilance and Epidemiology, Office of Health Affairs, and MEDWATCH.

Outcome: As a result of this cooperative effort, the healthcare community (through the MEDWATCH Listservs and Partners) was informed of the Internet availability of the transcript of the February 5, 1998, Anesthetic and Life Support Drugs Advisory Committee meeting. In addition, the working group drafted Questions and Answers based on the most frequently asked questions FDA had been receiving. This notification was released on May 6, 1998, and disseminated through the Internet, MEDWATCH Listservs and Partners, *FDA Medical Bulletin*, and the "From the Food and Drug Administration" monthly column in *JAMA.*

c. Satellite Broadcasts

Issue: Mechanisms were needed to get risk information about product treatments to more members of the healthcare community.

FDA Action: FDA works cooperatively with other PHS agencies (NIH, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Health Resources and Services Administration (HRSA), CDC, and the Indian Health Service (IHS)) to produce satellite downlink programs discussing important issues related to HIV/AIDS.

Outcome: The three broadcasts that have so far been aired discussed the Adult and Adolescent National HIV/AIDS Treatment Guidelines, the Pediatric Treatment Guidelines, and Adherence to Therapy and Prevention. These interactive video broadcasts provide a forum for discussion of important HIV/AIDS-related issues. Videotapes of these programs are made available to the public.

2. Other Communication and Information Dissemination Activities

a. Urgent News (hot topics) Communications:

FDA provides risk information to the healthcare community and consumers through its extensive outreach programs and the internet. Examples include:

i. Conference Calls

FDA routinely sets up conference calls with selected health professional organizations to convey information (e.g., on thalidomide) and solicit input (e.g., on heparinoids). Similar calls are set up with public organizations. One example that illustrates FDA's use of conference calls to communicate risk concerns is Norvir.

- Norvir

The Center for Drugs and OSHI participated in telephone conferences initiated by Abbott Laboratories. The purpose of the conferences was to announce and discuss manufacturing difficulties with Norvir (ritonavir) capsules. An undesirable crystal formed during the manufacturing process that affected the solubility of ritonavir and resulted in a shortage of Norvir capsules. The conference call included HIV/AIDS community participants and FDA staff. These types of conference calls have also been held to discuss issues such as expanded access to specific investigational drugs. This model generally allows for an open discussion among all three groups.

ii. Facsimiles

On the day information is issued, facsimiles are sent to:

- About 30 major health professional organizations, augmented with specialized lists when applicable
- 30 MEDWATCH Partner organizations that do not use e-mail
- Major countries, the European Union (EU), World Health Organization (WHO), Pan American Health Organization (PAHO), and the Food and Agriculture Organization of the United Nations (FAO). There are three international lists: food/veterinary products, drugs/biologics, and medical devices.
- About 50 consumer/women's health/patient organizations
- Media contact list that includes a minimum of 32 print and broadcast media outlets
- Congressional authorizing and oversight contacts, and other staffers when applicable

iii. Notifications

MEDWATCH expands the Center/Agency/manufacturer dissemination of medical product safety information through:

- MEDWATCH Partners Program: More than 140 health professional and industry organizations share information with their members. Many Partners link directly to the MEDWATCH website from their individual home pages.

- Listservs:

  Partner Listserv: Each Partner is directly notified by e-mail or fax.

  General MEDWATCH Listserv: More than 2,000 members, including more than 70 drug information centers, are directly notified by e-mail.

- MEDWATCH Website: The website contains the latest Dear Healthcare Professional letters, FDA safety notifications, and links to CDC's *Morbidity and Mortality Weekly Report* (MMWR) articles, particularly when the articles involve FDA actions.

b. General Communications

i. Websites

In addition to the MEDWATCH website, organizational units within FDA's Office of External Affairs target various stakeholders. For example, the OSHI homepage provides specific information on AIDS and cancer. The Office of Health Affairs targets the general healthcare community and the human subject protection community using links to centers and external sources of information. These FDA websites are organized in formats that make them easy for health practitioners and patients to understand and use.

The Center for Drugs maintains a website that is becoming a storehouse for communication about drug approvals. Approval letters, labeling text, and patient package inserts (when available) are generally posted within three days of the approval of a new drug. Since 1998, a consumer-oriented fact sheet written in question and answer format has also been posted for all new molecular entities (NMEs) that are approved. The complete review package is posted after the individual reviews have been redacted by the Freedom of Information (FOI) Office. Approval letters, labeling, and other information is also available through the Center for Drugs' Fax-On-Demand system.

The Center for Biologics maintains a website that provides consumers and health professionals with up-to-date information on biological drug and device approvals (including labeling and approval letters), recalls and market withdrawals of blood products, letters to industry and healthcare providers, product information sheets, and information on product shortages, product safety, adverse experience reporting, and transfusion-related fatality reporting. In addition, this website contains a list of all licensed biologicals and approved PMAs and 510(k)s cleared by the Center for Biologics. Consumers, healthcare providers, or any interested party can subscribe to one or all of the Center for Biologics' automated e-mail lists that distribute information about blood-related documents, recall of fractionated blood products, and/or new Center for Biologics documents. All of these documents are also available through the Center for Biologics' Fax-On-Demand system.

ii. Publications

Several Office of External Affairs (OEA) offices publish in the health professional literature. MEDWATCH particularly focuses on medical product safety in its publications. Through the MEDWATCH Continuing Education Article program, several peer-reviewed, journal quality articles with associated continuing education (CE) credit have been disseminated to the health professional community. These articles are designed to inform health professionals about the extent and spectrum of medical product-induced disease, and the importance of adverse event/product problem recognition and reporting. How FDA uses these reports to make regulatory decisions, the limitations/strengths of spontaneous reporting data, and how postmarketing risk assessment impacts clinical practice have been aspects specifically addressed as part of the CE article program.

Through the Office of Health Affairs, FDA publishes a monthly "From the FDA" column in *JAMA,* and periodic columns are published in the *American Family Physician Journal*. Centers often use these opportunities to address special concerns regarding product safety or to reenforce major safety concerns. In addition, individual articles, letters to the editor, and editorials are prepared as needed or requested for appropriate pharmacy, nursing, and medical journals. Center authors are sought for editorials and articles.

Articles on device problems are also published by the Center for Devices in professional journals. These articles are generated from data in the MDR system, epidemiological studies, and laboratory-based investigation. The MDR analyst staff has a regular column titled "Device Errors" in the *Nursing* journal.

OHA receives manuscripts for peer review from several journals, giving FDA a voice in whether or not articles are published, and if they are, to accurately state FDA positions. OHA coordinates FDA review and input for the CDC's MMWR. Many of the articles in the MMWR are co-authored by FDA.

Specific examples of Agency publications include:

- Protease Inhibitor Brochure

FDA approved three protease inhibitors between December 1995 and March 1996, and approved the fourth protease inhibitor in 1997. These drugs are generally considered to be the most potent therapeutic agents for HIV to date. In order for these drugs to be effective and to minimize the risk of resistance, it is important that these drugs are prescribed and taken in accordance with the products' approved labeling. Underdosing, noncompliance, or partial compliance with dosing regimens for these drugs may result in development of resistant strains of HIV that will not be susceptible to treatment with protease inhibitors. Additionally, the protease inhibitors are partially metabolized by the cytochrome P-450 oxidase system and have a potential for serious interactions with a large number of commonly prescribed drug products metabolized by the same pathway.

The complexity of the dosing regimens and the potential for serious drug interactions stimulated

the production of *The Protease Inhibitors* brochure. The original document and revision, a joint project of the Office of Special Health Issues (OSHI) and the Division of Anti-Viral Drug Products (DAVDP), were widely distributed and provided an important reference for the HHS HIV/AIDS Treatment Guidelines. This brochure continues to be updated and is currently only available on the Internet.

- Intravenous Immunoglobulin and Aseptic Meningitis Syndrome

In early 1994, FDA learned of a report from NIH that described a high rate of aseptic meningitis syndrome (AMS) occurring in patients being treated for neuromuscular diseases with high doses of immune globulin intravenous (IGIV). The patients had been receiving doses of 2 g/kg of IGIV, which is five to ten times higher than the normally recommended dosage. Six of 54 patients developed severe headache, meningismus, and fever within 24 hours of dosing. Cerebrospinal fluid (CSF) was consistent with AMS in four of the six.

Following this lead, 22 cases of IGIV-associated AMS that had been reported to the FDA were reviewed. Symptoms included fever, photophobia, and prominent painful headache. Twenty of the cases were associated with positive CSF findings, including leukocytosis (predominantly neutrophilic) and elevated protein. Unexpectedly, 19 of the reports indicated that normal doses of IGIV had been administered (0.2 - 0.4 g/kg). The patients had been treated by withdrawal of the medication and administration of analgesics. Of particular note was the characteristic time course of IGIV-associated AMS. The illnesses all began between 12 and 24 hours after administration, and recovery ensued within several days following withdrawal of the medication.

As a result of this work, FDA and NIH published two articles on IGIV-AMS simultaneously in the same journal (45,46). FDA also directed IGIV manufacturers to modify labeling to include a precaution statement about the occurrence of the syndrome.

- Hair Loss Following Hepatitis B Vaccine

In 1994, an epidemiologist in the Center for Biologics received a spontaneous telephone report of hair loss (alopecia) following administration of hepatitis B vaccine to a young girl. The signal was recognized and approximately 60 other spontaneous reports following vaccination were identified in FDA files, reviewed, and published in *JAMA*. The review led vaccine manufacturers to change product labeling, the VAERS program to flag other spontaneous reports of possible positive rechallenge during data entry, and CDC to conduct a confirmatory study in the Vaccine Safety Datalink.

- Renal Failure Due to Albumin in Plasmapheresis

The Center for Biologics received reports from MEDWATCH of the dilution of 25 percent human albumin with sterile water to produce a 5 percent albumin solution. Large volumes (1-2 liters) of the diluted albumin were used in plasmapheresis. Presumably because of the use of these large volumes of hypotonic solutions, extensive hemolysis occurred with consequent renal failure.

After a thorough search of FDA files, Center for Biologics staff summarized this situation and published it in the *FDA Medical Bulletin*, the *New England Journal of Medicine*, and other journals. Manufacturers of human albumin were directed to change their product labels to warn against the practice of dilution with sterile water and to suggest use of normal saline solution or other safe alternatives.

- Other Publications

The Center for Drugs helped develop four brochures in partnership with various national organizations last year. These include *Medicine: Before You Take It, Talk About It*, with the National Council on Patient Information and Education (NCPIE); *Making Your Medications Work Better* and *Questions to Ask Your Pharmacist*, with the American Pharmaceutical Association (APhA); and *Food and Drug Interactions*, with the National Consumers League (NCL).

iii. Periodic Mailings

OEA offices prepare periodic mailings of Agency documents (e.g. press releases, talk papers, *FDA Medical Bulletin*, Dear Colleague letters, meeting announcements). There is no specific schedule for these mailings. For example, OHA maintains a list of more than 200 major health organizations and does a mailing every 2 to 3 weeks. OSHI maintains a list of AIDS and cancer contacts and generally does a mailing every month. The Office of International Affairs prepares mailings for embassies and counterpart agencies in other countries on a quarterly basis. OLA provides agency documents to congressional authorizing and oversight contacts, and other staffers when applicable.

iv. Presentations

The OEA and the Centers present, participate, and exhibit at health professional and consumer meetings (e.g., National and District Consumer Forums, health professional organization meetings, roundtable meetings) and provide information through formal and informal telephone calls and face-to-face meetings.

v. MEDWATCH — other activities

In addition to the MEDWATCH Partners program, MEDWATCH works with other organizations including the United States Pharmacopeia (USP), the National Coordinating Council (NCC) for Medication Error Reporting and Prevention (MERP), PhRMA Clinical Safety Surveillance Committee, PhRMA Education and Research Institute (PERI), the Drug Information Association (DIA), the Joint Commission on Accreditation of Health Care Organizations (JCAHO), and the Uniformed Services University of the Health Sciences (USUHS). Activities with these organizations range from ongoing educational activities (e.g., PERI, USUHS) to cooperation on adverse event and/or product problem reporting (e.g., NCC MERP, USP) to liaison regarding requirements and/or stipulations for adverse event and/or product problem reporting (e.g.,

PhRMA Clinical Safety Surveillance Committee, JCAHO). MEDWATCH also presents postmarketing surveillance-related lectures at local and national meetings, publishes continuing education articles on adverse event reporting, links its website to CDC's MMWR articles when the articles involve FDA actions, and generates (in cooperation with the Center for Drugs) monthly summaries of the latest safety-related drug labeling changes.

vi. Information Branch

The Drug Information Branch of the Center for Drugs answers approximately 2,000 phone calls a month from consumers, healthcare providers, and other interested parties. The Executive Secretariat Team answers letters from the general public. Both groups are also seeing a large increase in the number of e-mails they are receiving from the public. The Center for Drugs also holds hot topics briefings for the public affairs specialists in the FDA field offices.

vii. The Center for Devices and Clinical Practice Community

The Center for Devices has a long history of involving the clinical practice community in assessment of patterns of injuries and device failures and development of educational tools to address them. Examples of these tools include publication of brochures, checklists used by professionals in their everyday practice, guidance to industry for the development of safer products, guidance to users on injury avoidance practices, manuals to assist the industry in their risk communication in labeling and other interactions with their customers, and a series of videotapes that provide instructions for a variety of medical devices.

The Office of Device Evaluation in the Center for Devices has initiated a number of types of outreach to and contact with various segments of the clinical community. These efforts include sessions at the annual meetings of organizations such as the American Academy of Ophtholomology (AAO), the North American Society for Pacing and Electrophysiology (NASPE) and the Radiological Society of North America (RSNA). These efforts also include participation in standing meetings with the technology assessment, regulatory affairs, or FDA issues committees of the Society for Cardiovascular Interventional Radiology (SCVIR), the American College of Gastroenterology (ACG), and the American Society for Gastrointestinal Endoscopy (ASGE).

In addition, the Center for Devices is a founding member of two unique groups that bring together the regulated industry, the research community, the practice community, and the regulatory agency. One group is called the Orthopedic Forum, and meets quarterly to identify areas needing input from the various groups to further the development of new technologies. This group provides a platform for discussion and has been instrumental in developing draft guidances to present to the Agency. The second group is the Baltimore Round Table (initiated by the Baltimore district) that addresses issues of impact on the in vitro diagnostic area, and includes all of the major trade associations, as well as representatives from the Center for Biologics, the Center for Devices, and ORA. In coordination with NIH, specifically the National Institute of Dental Research and the National Eye Institute, forums have been convened with industry and the

clinical community to address technology development and the need for coordinated efforts among all of the stakeholders.

APPENDIX I

Risk Evaluation Examples

Effects of Risk Communication on Physician Prescribing Behavior

1. The Center for Devices Survey Following a Public Health Advisory

Issue: On March 20, 1998, the Center for Devices distributed an FDA Public Health Advisory of interference between digital TV transmissions and medical telemetry systems. FDA wanted to evaluate the format and content of the Advisory to assess the effectiveness of the communication.

FDA Action: The Center for Devices mailed a survey questionnaire to a randomly selected sample of 308 advisory recipients. To maximize response rates, two additional mailings of the survey were directed at nonrespondents.

Outcome: FDA received a total return of 190 questionnaires, of which 183 were determined to be valid completions, for a response rate of 59.4 percent. Of the respondents, approximately 98 percent felt that the problem addressed in the advisory was clearly identified and easily understood. The respondents stated that the information was both timely (93 percent) and useful (86 percent). They also felt the actions for reducing risk were clearly explained (97 percent). About 36 percent of the respondents stated they were aware of the interference problem prior to receiving the advisory. Approximately one-third of the respondents first became aware of the problem from a professional bulletin. About 37 percent of the sample group reported they had taken actions to eliminate or reduce the risk as a result of the advisory. The most commonly reported reason for not taking action was that the subject matter of the advisory was not applicable. Most respondents would prefer to receive future alerts as they are currently distributed — printed and mailed (75 percent). Only 10 percent of the sample group preferred to receive future bulletins electronically (Internet mailing list).

The Center for Devices has found such surveys to be helpful in determining the effectiveness of Public Health Advisory risk communications and whether improvements in the process need to be addressed.

2. Population-Based Data Resource for Serevent

The effect of risk communication or other regulatory intervention on physician prescribing behavior can be measured using population-based data resources. As described in Appendix C,

FDA uses IMS health products and services to monitor the effect of regulatory actions by the Center for Drugs and a variety of other users. Measuring physician prescribing behavior can help FDA evaluate its communication methods and make changes in the process.

Issue: Communicating risks may not always have the intended effect. Following its market introduction, FDA received a number of reports of fatal asthma attacks in patients using Serevent (salmeterol), a long-acting beta-agonist approved for the treatment of stable asthma. FDA was concerned that the product was being used to control patients with unstable asthma or was being substituted for other asthma medications inappropriately. A Dear Healthcare Professional letter was sent informing practitioners that Serevent should not be used for acutely worsening asthma, that it was not a replacement for short-acting bronchodialators, and was not a substitute for anti-inflammatory medications.

FDA Action: FDA used data from New York Medicaid to measure the effect of this letter. The computerized pharmacy claims records of each patient who filled a prescription for salmeterol within the database were examined for the presence of an albuterol claim in the 3-month period prior to their first salmeterol prescription.

Outcome: The proportion of patients without prior albuterol use was compared for the time interval before and after the letter. Prior to the Dear Healthcare Professional letter, 75 percent of new salmeterol users had no prescriptions for albuterol during the 3-month interval preceding their salmeterol use. After the letter, this estimate fell to 67 percent, suggesting that physician prescribing behavior within this Medicaid database had not changed in a clinically meaningful way.

Although the evidence did not clearly demonstrate an on physician prescribing patterns, FDA has noticed that the number of reports of fatal asthma attacks fell to below the number of reports prior to the Dear Healthcare Professional letter and has remained low. In addition to monitoring the number of events, FDA discussed its evaluation results and concerns with the product sponsor. The sponsor also followed up with physicians to ascertain that the information was appropriately affecting prescribing habits and is currently conducting a large phase-4 controlled trial to address the issue of mortality risk in patients who use the product in accordance with the label.

Summary: This example illustrates that continued efforts are needed to further evaluate FDA's risk assessment tools and subsequent interventions to ensure effective communication efforts and processes. As part of this continued effort, FDA is evaluating other interventions and is currently performing a study within the Center for Drugs' Cooperative Agreement Program to measure the effect of a series of Dear Healthcare Professional letters relating to liver transaminase monitoring in patients treated with troglitazone (Rezulin). This study will assess the performance of baseline and monthly transaminase monitoring using computerized billing claims for laboratory testing. The results from this study should contribute to regulatory policy relating to this product.