EXECUTIVE SUMMARY

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
May 1999

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

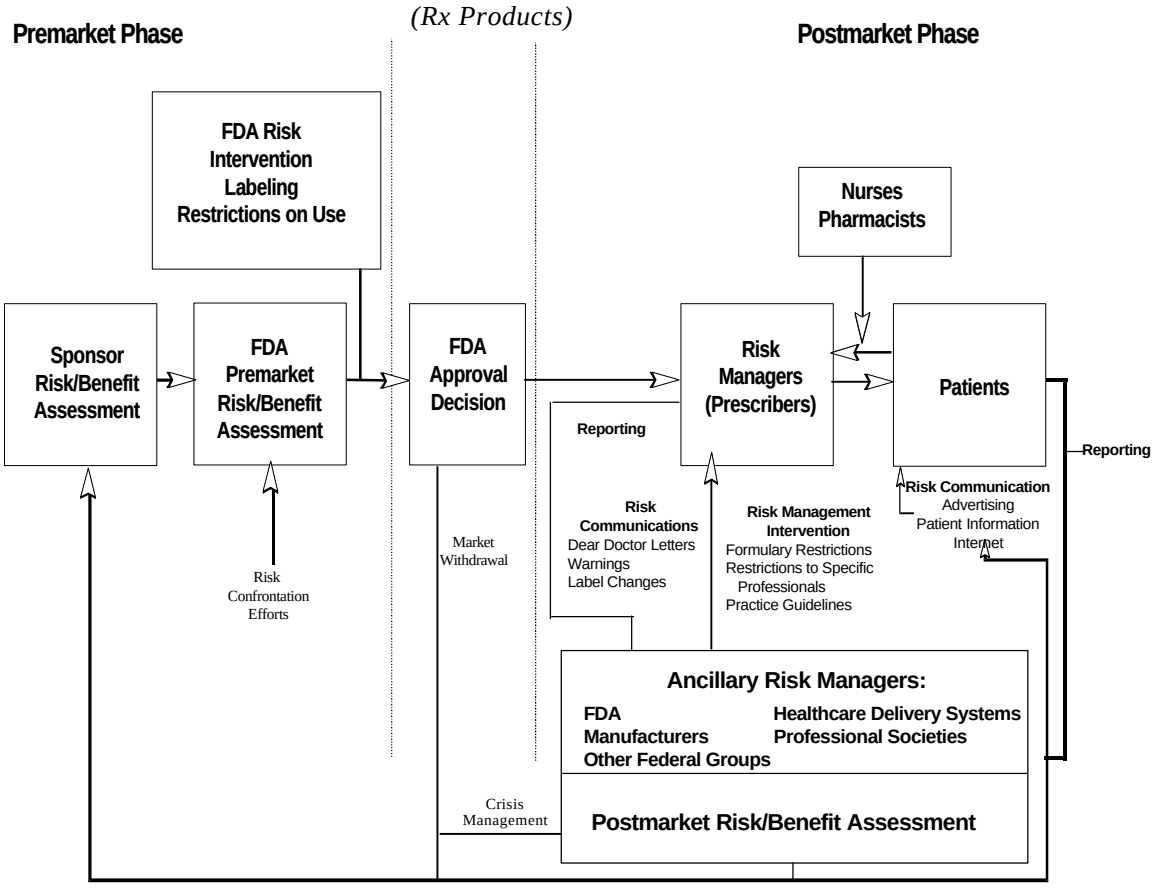
The time is right for a new framework

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



Not everyone's role is clearly defined

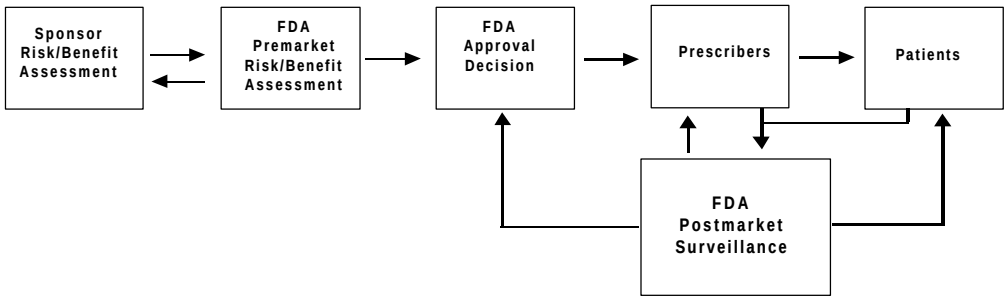
Although medical products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. All participants in the medical product development and delivery system have a role to play in 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

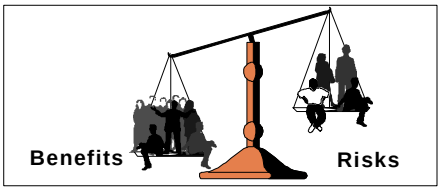
(Rx Products)



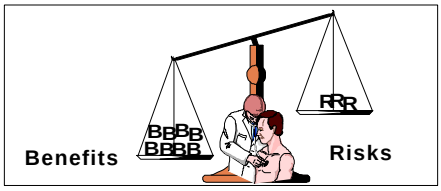
The Agency approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use. A major goal of the premarketing review is to ensure that products are truthfully and adequately labeled for the population and use. Labeling is given considerable 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.

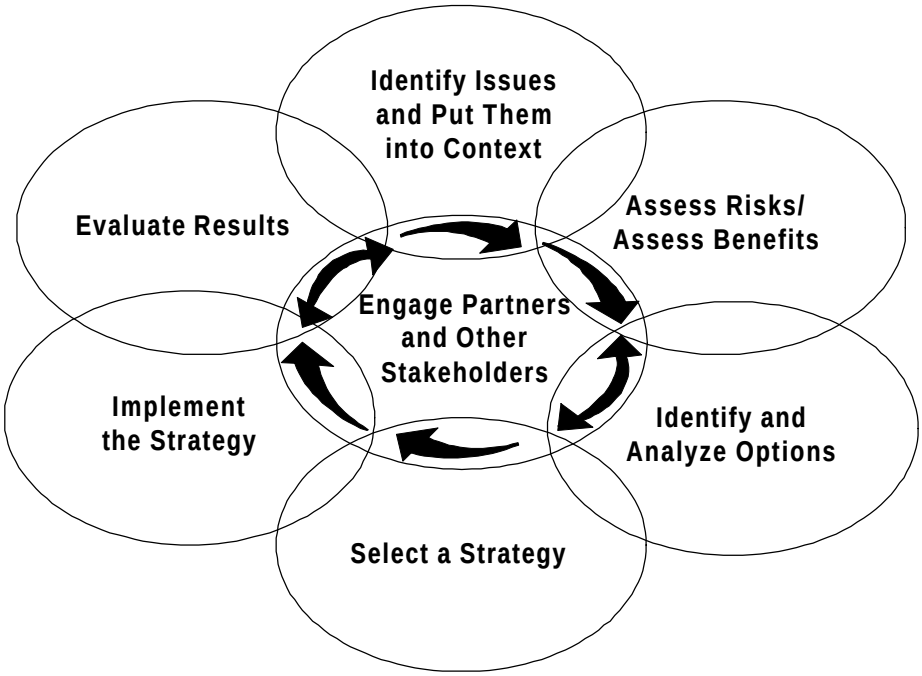
Although the FDA's role is fairly clear, the roles of some of the other participants are less clear. This is because what began as individualized care by one practitioner has evolved into a complex system of risk management that now involves manufacturers, the FDA, practitioners, many other elements 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

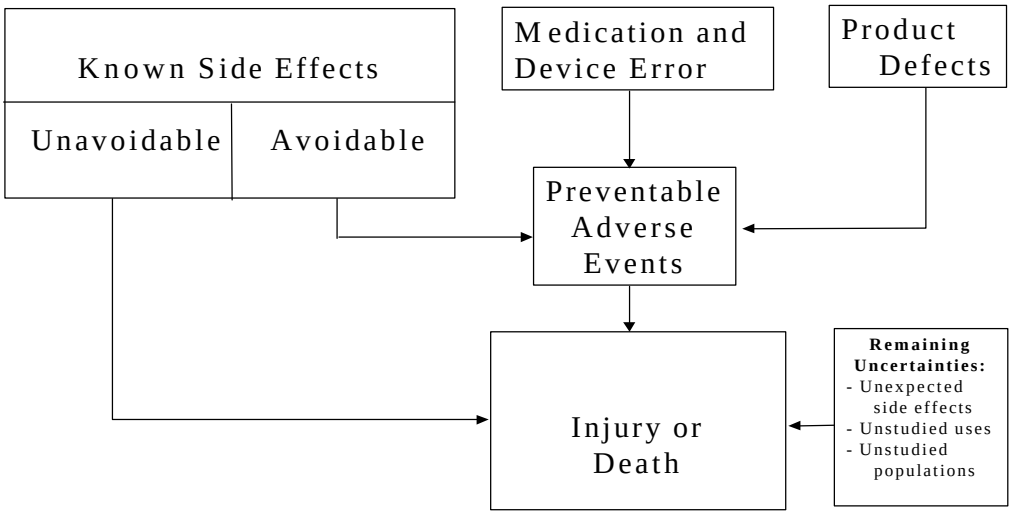
The Task Force recommends that FDA take the opportunity to engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all participants in 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

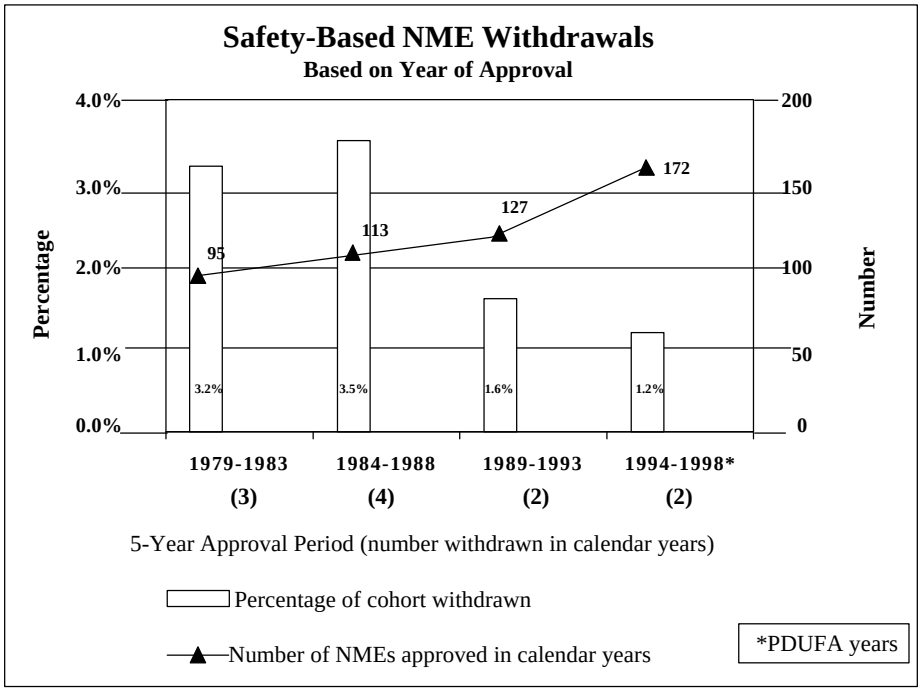
[4] A number of terms are used to describe an adverse event, including *adverse drug reaction* (ADR), *adverse experience*, and *adverse effect*. In this report, the term *adverse event* is used in most cases to avoid confusion.

[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.

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[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, 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.

Slowing a rapid market rollout for some products when time-tested 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 changing 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 ends 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.