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Report to the Chairman, Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Operations, House of Representatives

April 1990

FDA DRUG REVIEW

Postapproval Risks 1976-85

GAO/PEMD-90-15

GAO

United States
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Program Evaluation and
Methodology Division

B-235944

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The Honorable Ted Weiss
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

In response to your request, we are submitting this report describing postapproval risks for drugs approved by the Food and Drug Administration between 1976 and 1985. The report identifies drugs for which serious risks arose after approval for marketing, and it investigates the relationship of these risks to some attributes of the drugs and the review process.

As we arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of the report. At that time, copies of the report will be sent to the Secretary of the Department of Health and Human Services and the Commissioner of the Food and Drug Administration, and we will make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Dr. Michael J. Wargo, Director of Program Evaluation in Physical Systems Areas, at (202) 275-3092. Other major contributors to this report are listed in appendix VI.

Sincerely,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

Assessing the efficacy and safety of a drug to obtain Food and Drug Administration (FDA) approval is a lengthy and complex process. But even after approval, many additional risks may surface when the general population is exposed to a drug. These risks, which range from relatively minor (such as nausea and headache) to serious (such as hospitalization and death) arise from the fact that preapproval drug testing is inherently limited. The extent of postapproval risks and the reasons they go undetected during preapproval testing, however, have not been analyzed.

The Chairman of the Subcommittee on Human Resources and Intergovernmental Relations of the House Committee on Government Operations asked GAO to study the frequency and seriousness of drug risks identified after FDA approval for marketing and to examine some of the characteristics of these drugs as a first step in understanding why these additional risks occur.

Background

The drug approval process begins with the submission of an "investigational" application, when a drug company applies to FDA for permission to test the drug in humans. Then, when the clinical studies involving humans provide evidence of a particular drug's beneficial effect at an acceptable level of safety, the company submits a new drug application (120 were submitted in 1986) to FDA for approval of the drug for widespread use. The agency subsequently reviews all evidence pertaining to the drug's efficacy and safety. If it finds the cumulative evidence acceptable, FDA approves the drug for marketing (after, on the average, 29 months of review).

The preapproval human clinical trials for a drug involve testing with a relatively small sample of the potential user population under controlled conditions that limit the extent of risk assessments. However, when therapeutic benefits appear to outweigh the estimated potential risks, the new drug is approved as soon as possible for the benefit of those who can use it. After FDA approves the drug for marketing, it is then used by patients under conditions much less controlled than those that prevailed during testing.

When a company markets an approved drug, it is required by law to include directions for its use—as well as warnings, precautions, and adverse reactions—on the drug's label. Postmarketing surveillance then identifies potential adverse reactions not included on the original label that are discovered after marketing is begun. If an adverse reaction is

found to be linked to the use of a drug, its label is changed to include the additional risk. GAO reviewed the label changes for all 209 new drugs FDA approved between 1976 and 1985 in order to determine the frequency and seriousness of the additional risks linked to these drugs after their initial approval. GAO plans to continue its examination of the factors underlying the occurrence of serious postapproval risks in FDA-approved drugs.

Results in Brief

In studying the frequency and seriousness of risks identified after approval, GAO found that of the 198 drugs approved by FDA between 1976 and 1985 for which data were available, 102 (or 51.5 percent) had serious postapproval risks, as evidenced by labeling changes or withdrawal from the market. All but six of these drugs were currently marketed as of September 1989 and are deemed by FDA to have benefits that outweigh their risks. The serious postapproval risks are adverse reactions that could lead to hospitalization, increases in the length of hospitalization, severe or permanent disability, or death. These adverse reactions resulted in a substantial change in the labeling of the drugs, typically either limiting the population for which they are intended or adding major warnings or precautions for their use.

The number of serious postapproval risks is small when compared to the number of adverse reactions that had been identified at the time of approval. GAO did not attempt to determine the reasons why the risks emerged (or whether they could have been identified during preapproval testing), the extent to which patients were exposed to them before they were identified, or the number of patients affected. However, these findings make clear that further understanding is needed of the characteristics associated with these additional risks and why they arose.

Principal Findings

The serious postapproval risks identified in studying their frequency and seriousness involved a wide variety of adverse reactions, including heart failure, myocardial infarction, anaphylaxis, respiratory depression and arrest, convulsions, seizures, kidney and liver failure, severe blood disorders, birth defects and fetal toxicity, and blindness. These adverse reactions occurred over many drug classes. GAO found that in 12 of 22 classes more than 50 percent of the drugs approved had serious postapproval risks. The 12 classes are cardiac drugs, psychopharmacologic drugs, drugs to combat drug abuse, antibiotics, fertility and antifertility drugs, metabolic and endocrine drugs, ophthalmic drugs,

antiparasitic drugs, oncology drugs, anti-inflammatory drugs, anesthesia drugs, and surgical drugs. The degree of additional risk varied: It was more serious and occurred more often for some drugs than for others, with approximately one quarter having serious postapproval risks affecting three to five body systems (including cardiovascular, respiratory, central nervous system, renal, and gastrointestinal). Additional risks in a body system fall along a spectrum that includes other less severe adverse reactions. (See pages 24-41.)

In examining some characteristics of drugs approved by FDA, GAO found several that are associated with the presence of serious postapproval risks. Drugs that appeared on FDA's postmarketing surveillance list because of adverse reactions not present on the current label were over 10 times as likely to have serious postapproval risks as those that did not. Drugs that were reviewed for use in children were more than twice as likely to have serious postapproval risks. Drugs approved between 1976 and 1980 were almost three times as likely to have serious postapproval risks as those approved between 1981 and 1985, although some evidence suggests that GAO's assessment for the latter period may be low (see pages 51-53). GAO also found that among drugs approved in fewer than 4 years, those that turned out to have serious postapproval risks had generally been approved by FDA in a shorter time than those without such risks. The class of a drug may also be related to the emergence of serious postapproval risks. (See pages 42-56.)

Recommendation

GAO recommends that the Commissioner of FDA establish formal procedures to evaluate postapproval risks for new drugs and use this information in premarketing review and postmarketing surveillance. GAO believes that such procedures would contribute to better and more timely drug labeling. GAO believes that FDA, in implementing this recommendation, should build upon the steps followed in this report: (1) identifying serious and nonserious postapproval risks, (2) enumerating the risks by drug class, (3) identifying the body systems affected by the risks, and (4) comparing the additional risks with those identified at the time of approval. The Commissioner should also try to estimate the population exposed to the additional risks and assess their significance in terms of expected fatalities and morbidity.

Agency Comments

While agreeing that it is important to know whether the current drug review process may overlook serious risks, HHS objected to GAO's methodology. The department was also concerned that this report will unnecessarily alarm consumers, causing some to reject the use of lifesaving drugs out of fear of adverse events that might occur only in extremely rare instances, and that it could create a misleading impression of the drug review process, by identifying drugs as having serious postapproval risks that could not have been so identified in the drug review process. Also, HHS did not concur with GAO's recommendation, indicating that it was vague and that it assumed FDA could somehow anticipate the unknown.

GAO believes the study methodology was sound and, consequently, no substantial changes have been made in the findings, conclusions, or recommendation. However, GAO has modified the presentation in certain parts of the report to clarify the language and to avoid misunderstandings about the research performed (that is, the questions posed and the methodology for answering them).

With respect to HHS's view that consumers will be unnecessarily alarmed by this report, GAO has noted that 96 of the 102 drugs identified as having serious postapproval risks were currently marketed as of September 1989 and thus are deemed by FDA to have benefits that outweigh their risks, despite the additional risks that have been identified. GAO does not dispute FDA's assessment of benefits and risks. What is in question here is the degree to which careful analysis can help in reducing predictable risk to the consumer.

HHS's comments are reproduced as appendix V to this report. GAO's response to each point is contained in appendix V and presented at other appropriate places in the body of the report.

Contents

Abbreviations

FDA	Food and Drug Administration
GAO	General Accounting Office
HHS	Department of Health and Human Services
MART	Monitored Adverse Reaction Tracking

Introduction

The Food and Drug Administration (FDA) approves a new drug for marketing only after a complex review process that can last several years. There is always an inherent trade-off between the need for more information about a drug's risks and the hope of bringing its benefits to its intended population. In other words, the drug development process accepts the possibility that rare (for example, 1 in 5,000) serious adverse reactions may occur in the use of a drug after it is approved. The extent to which serious additional risks arise after approval and whether more can be done during the review phase to identify them are issues that warrant study.

The Subcommittee on Human Resources and Intergovernmental Relations of the House Committee on Government Operations asked us to study these issues. This report documents the first step of our evaluation: it provides information on the frequency and seriousness of risks that surface after FDA's review and approval of new drugs.

The Study Basis and Its Evolution

The principal objective of our overall study is to evaluate the components of the drug review process that relate to the safety of a drug. Because of limitations in the extent of clinical trials performed during a drug's development, not all the benefits and risks are identified before its approval. More information about a drug almost always emerges after its approval. This information is identified through continued research on the drug, through FDA's postmarketing surveillance, and sometimes through postapproval research required by FDA as a condition of approval. The identification of additional risks after approval occurs mostly from FDA's postmarketing surveillance.[1] For purposes of this study, we consider only drug risks identified after approval (which we refer to as postapproval risks).

The examination of the relationship between the review process and postapproval risks is very complex. We surveyed pertinent literature and discussed the nature of the relationship with FDA officials and academic and private sector experts to determine the scope of such a study. We determined that the study would first require defining serious postapproval risks and identifying factors in the FDA approval process that might be associated with such risks. Following this, pertinent data

[1]New uses or indications for a drug constitute additional benefits identified after initial approval. The risks corresponding to these new uses are also separate from the initial approval and hence are outside the scope of this study.

would have to be extracted from voluminous records accumulated during FDA's review process and then analyzed.

Because of the complexity of our study, we decided, with the agreement of the Subcommittee, to proceed in two phases, first developing information about postapproval risks for a number of drugs and, second, examining the relationship between FDA's approval process and the postapproval risks identified for certain drugs. This report presents the results of the first phase.

Before it approves a drug for marketing, FDA weighs the evidence, taking into account whether the benefits outweigh the risks. After approval, more information on benefits and risks is acquired once the drug is marketed and is in wider use than during the clinical testing in limited groups. If the additional risks are deemed to result in total risks outweighing the benefits, the drug is withdrawn from the market. This occurred for 6 of 209 drugs approved between 1976 and 1985. More typically, the additional risks are reflected on revised drug labels.[2]

FDA does not analyze the overall change in risks for all the drugs it approves. The agency focuses only on the change in risk for a particular drug and does not attempt to determine either the frequency and seriousness of postapproval risks for all drugs or the sources or reasons for these risks. And yet these issues are of critical importance to the public safety and, hence, to FDA's managers as well as the Congress. Usually, these issues are debated only in connection with individual drugs. For example, the Congress may hold hearings on the decisionmaking process for a particular drug whose postapproval risks have made the headlines. Or, the public expresses concern about the time it takes to approve a new drug to combat a specific disease such as AIDS. These issues are also addressed implicitly, but typically without empirical data, in attempts to improve the efficiency of FDA's review process and to ensure that drugs are made available as soon as possible.[3]

We undertake to answer two questions in this report: (1) What is the occurrence, overall, of serious postapproval drug risks? (2) What attributes of drugs and the FDA review process are associated with these additional risks? The attributes examined in this report are a limited set of

[2]Labels summarize a drug's benefits and risks and provide guidance to physicians prescribing it.

[3]In particular, see the preambles to proposed changes in regulations for new drugs and new drugs being investigated (50 Fed. Reg. 7452 (1985), 52 Fed. Reg. 8798 (1987), and 52 Fed. Reg. 19466 (1987)).

those that describe drugs and the review process; we will examine the relationship between postapproval risks and a larger number of attributes in a later report.

Background

To put our study into perspective, we need to describe some aspects of FDA's review process, particularly the role of a drug's label. Under current law, a company must provide evidence of a drug's efficacy and safety for its intended use prior to marketing. (21 U.S.C. 352(f), 355(b), (d)) Specifically, the law requires

- substantial evidence of the effectiveness of a drug for its proposed uses,
- evidence that the drug is safe and that all tests reasonably applicable to an assessment of safety have been performed, and
- labeling that provides the physician with adequate direction for the safe and effective use of the drug.

The evidence submitted to FDA in fulfilling the first two requirements is generated in clinical trials. This evidence is then used to construct the applicable labeling when the drug is approved for marketing.

In the course of its development, a drug enters the "investigational new drug phase," during which several studies (clinical trials) are conducted with a limited number of human subjects. When a company determines (usually in conjunction with FDA) that it has obtained sufficient evidence of the drug's efficacy and safety and has initiated clinical trials involving a larger number of human subjects, it applies to the agency for approval. The drug then enters the "new drug application phase." FDA has 6 months to rule on the application (by approving or disapproving it), although the duration is usually extended by mutual consent and averages about 29 months. After approval, FDA may request further studies to resolve additional efficacy and safety issues and, in any event, maintains postmarketing surveillance on all drugs.

The Drug Review Process

FDA's drug review process examines protocols and results of the clinical trials for a drug from medical, pharmacological, chemical, and statistical perspectives. Initially the focus is on the results of individual trials and increasingly on results across trials. An FDA medical officer prepares a summary of these results, which is used as the basis for the final approval decision. The main focus of this review is on the efficacy of the drug, with as much consideration of the issue of safety as is possible.

Drug Labeling

The benefits and risks associated with a drug are capsulized in the drug's label. The label is required by regulation to include information under the following headings (in this order): description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, overdosage, dosage and administration, and how supplied. (21 C.F.R. 201.57) (A brief description of each of these sections is provided in table 1.1.) A draft label is submitted as part of the new drug application, undergoes revision during review, and is made final in the approval letter, which is the final step of the review process. Changes made to a label after FDA approval constitute a basis for examining benefits or risks identified with wider use of the drug during marketing.

Table 1.1: Contents of Major Label Sections

Section	Contents
Description	The name, dosage form, route of administration, ingredient information, and chemical formula of the drug
Clinical pharmacology	Actions of the drug in humans, including degree and rate of absorption, pathways of biotransformation, rate or half-time of elimination, concentration in body fluids, degree of uptake by a particular organ or in the fetus, and passage across the blood-brain barrier
Indications and usage	The disease, condition, manifestations, or symptoms relieved or adjunctive use of the drug, including specific subgroups of a larger population with a disease (identifying specific tests), safety considerations restricting the use of the drug, specific conditions for long-term use, uses for which the drug is ineffective (if there is a common belief that the drug is effective for such uses), and comparisons with other drugs
Contraindications	Situations in which the drug should not be used (known hazards)
Warnings	Serious adverse reactions and potential safety hazards, resulting limitations in use, and steps to be taken if they occur, with special problems (those leading to death or serious injury) placed in a prominently displayed box
Precautions	Any special care to be exercised for safe and effective use, including information for patients, laboratory tests, drug or laboratory test interactions, carcinogenesis, mutagenesis, impairment of fertility, pregnancy effects (including teratogenic and nonteratogenic effects), effects on labor and delivery, use in nursing mothers, and pediatric use
Adverse reactions	Undesirable effects reasonably associated with the use of the drug or unpredictable in their occurrence, including those in the same pharmacological or chemically related class, ordered by frequency and severity
Drug abuse and dependence	Types of abuse that can occur and adverse reactions pertinent to them, psychological and physical dependence related to the drug's use (including the quantity and period of time when the effect occurs), and effects of chronic abuse or abrupt withdrawal
Overdosage	The signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment, including the amount ordinarily associated with symptoms of overdosage or likely to be life-threatening
Dosage and administration	The recommended usual dose, dosage range, and an upper limit beyond which safety and effectiveness have not been established, including intervals recommended, method of adjusting dosage, usual duration of treatment, modification of dosage needed in special patient populations, and directions for dilution, preparation, and administration of the dosage form
How supplied	The available dosage forms, including strengths, available units, and information to facilitate identification of the dosage forms

Although the general contents of a label are specified by regulation for the time of approval, they are subject to change after the drug is approved. Changes in labeling reflect additional information about the risks and benefits of using the drug. Additional risks are identified largely through postmarketing surveillance, which is intended to detect previously unsuspected adverse reactions to a drug. FDA maintains a sophisticated adverse reaction reporting system to gather and analyze this information. This system helps identify additional risks of a drug and may lead to changes in its labeling.

Postmarketing Surveillance

Postmarketing surveillance of drugs consists primarily of examining reports of adverse drug reactions submitted by drug companies, physicians, hospitals, and consumers. FDA maintains a computerized system of reports of each adverse reaction incident since 1969.[4] This system, along with such other sources of information as the postapproval research required by FDA at the time of approval, constitutes the basis for changes in a drug's labeling.

Label changes are made only after a period during which (1) a drug is approved, (2) actual marketing begins, (3) adverse reactions are recognized and submitted, (4) the latter are analyzed, and (5) a labeling change is made. In general, it is thought that the most serious postapproval risks are identified by 3 years after the date of approval.

Through the use of a variety of criteria, FDA's postmarketing surveillance is designed to recognize adverse reactions that are not but should be noted on a drug's current labeling. These criteria lead to what are called monitored adverse reactions, which are maintained in a tracking system known as MART.[5] Approximately 45 to 85 drugs are on the monthly MART report; some are dropped and some are added each month. Drugs are usually removed from the MART report because a change in labeling has been made or the observed adverse reaction has proven not to be associated with the drug and thus requires no further examination.

[4]The quality and utility of the information produced by this system and the difficulties in interpreting the results have been the subject of much attention. In addition, some postapproval risks may not yet have been identified for particular drugs. These issues, however, are beyond the scope of our study.

[5]This particular system (Monitored Adverse Reaction Tracking) has been operating in its present form since December 1985, but adverse reactions have been monitored since 1965.

Serious Postapproval Risks

Many changes to the labeling of a drug do not pertain to risks, or they are associated with negligible postapproval risks. Thus, we need to distinguish drugs with nominal additional risks from those for which serious additional risks were identified after approval. The description of these postapproval risks and the characteristics of the drugs for which they occur constitute the primary focus of this report.

Our criteria for determining that serious postapproval risks have occurred for a drug include (1) withdrawal of the drug from the market for safety reasons, (2) identification of the drug in the FDA Drug Bulletin as having a serious postapproval risk, or (3) major (specific) changes in the labeling, primarily in the warnings, contraindications, precautions, or adverse reactions sections of the label (frequently, the addition of a boxed, bold, or italicized warning).[6] Changes in other sections of a label are generally not major; however, we examined all changes in labeling for the drugs we reviewed. (Criteria for serious labeling changes are discussed below.) A drug will meet our risk criteria only if the labeling change reflects a serious medical problem.

In addition to looking at actual changes in labels, we tried to identify drugs for which such changes are imminent. As noted earlier, in connection with postmarketing surveillance, FDA's MART system may identify drugs for which evidence of serious postapproval risks is accumulating from adverse reaction reports. Therefore, we extended our assessment of labeling changes to include examining the MART reports to identify drugs with a strong likelihood of having a labeling change of a type that would constitute a serious postapproval risk.

Objectives, Scope, and Methodology

Objectives

At the beginning of this chapter, we described our overall approach for examining the relationship between FDA's approval process and the postapproval risks identified for certain drugs. This report describes the results of the first phase. In particular, the questions we addressed in this phase are

[6]It is important to note that postapproval risks are expected for any drug; new evidence of clinical experience, not available until after approval, is part of the continuing evaluation of a drug's safety.

1. What is the occurrence, overall, of serious postapproval risks?

2. What attributes of drugs and the FDA review process are associated with these serious postapproval risks?

The attributes examined here are a limited set of those that describe drugs and the review process. The purpose is to search for the factors that are related to postapproval risks, rather than look for deficiencies in the review process.

Scope

FDA receives a large number of applications for the investigation of new drugs and supplemental applications for review each year (5,146 in 1986, of which 120 were new drug applications). Investigational drugs are still in development, may not be approved for marketing, and hence were excluded from our study. New drug applications seek approval for new chemical entities; new salts, esters, or derivatives; new formulations; new combinations; or an already marketed product (by another company). Supplemental applications propose a particular change in an existing drug application—that is, for drugs already approved—such as labeling changes or a new indication for use. Since all but the new chemical entities are concerned with drug components already marketed, we focused our study on the new chemical entities.

We selected for review all new chemical entities approved during 1976-85. We chose 1985 as the final year in order to ensure that drugs had sufficient exposure on the market after approval to have accumulated adverse reactions. As we stated above, most unsuspected adverse reactions, particularly those that are serious, are expected to emerge within 3 years of approval. We asked FDA to provide us with a list of new chemical entities approved during the time period of interest. The 209 drugs used in our study are listed in appendix I.

To determine the postapproval risks of a new drug, we compared the original label (that is, the label at the time of approval) and the most recent label. Although ultimately our study is intended to include characteristics of the review process and the clinical testing for a drug, in the attempt to identify predictors of whether a drug is likely to have serious postapproval risks, these data require an examination of the voluminous records accumulated during the review process. For the work reported here, we collected only a limited set of data, guided primarily by their availability and reliability for each of the drugs. Thus, we considered only attributes such as therapeutic class, drug type, the

length of time from receipt of a new drug application until its approval, and whether the drug had appeared on FDA's MART list. It is important to note that these attributes describe only a few aspects of drugs and the review process; therefore, our findings in this report do not address the effectiveness of the review process.

Methodology

As mentioned above, we asked FDA to provide us with a list of new chemical entities approved between January 1, 1976, and December 31, 1985. This list was generated by using FDA's Centerwide Oracle Management Information System and validated using other data sources. We then used this information system to retrieve the date on which the new drug application was submitted and the date it was approved, whether it was withdrawn from the market, the therapeutic class of the drug, and its therapeutic gain (FDA's assessment). We also gathered information about several characteristics of the drug, such as whether it was an "orphan" or designated orphan drug.[7] Other characteristics were whether it was already marketed overseas, whether it was subject to unique conditions of approval, whether it was considered a sensitive drug, whether it had important problems in toxicity, and whether it was reviewed for use with children.

We requested from the FDA Division of Drug Information Resources a copy of the original and the most recent label for each drug. We also requested the Summary Basis of Approval for each drug. This document summarizes the basis upon which FDA judged the efficacy and safety of the drug and also contains the labeling at the time of approval. Neither source provided either the original or most recent labeling for all drugs. We supplemented these sources by searching for the earliest and the most recent labels appearing in the Physician's Desk Reference, an annual compendium of information on major pharmaceutical and diagnostic products, the contents of which are required by law to follow the approved label verbatim.

As a result of these efforts, we were able to obtain labels suitable for comparison for 198 of the 209 drugs. For the 11 other drugs, 4 were never marketed; 2 were marketed for only a short time and then withdrawn, apparently for economic rather than safety reasons; 2 have not been marketed for some time and did not have up-to-date labels; and 1

[7]An orphan drug treats a disease or condition generally affecting fewer than 200,000 persons in the United States; a designated orphan drug is one that has been formally identified as an orphan drug by FDA, giving the sponsor certain economic inducements to market the drug (such as exclusive approval for 7 years).

was not considered a prescription drug. For the 2 other drugs, we were not able to obtain suitable labels for comparison.

To assess whether a drug had a serious postapproval risk, we first identified drugs that were mentioned in the FDA Drug Bulletin as having serious new adverse reactions. We then identified drugs indicated by FDA's management information system as having been withdrawn from the market. Finally, we examined the labels of the drugs; this constituted the most significant amount of our work.

In assessing the labels for whether a drug had a serious postapproval risk, we began by comparing the initial and the most recent labels, word for word. We compiled a list of all differences between the two labels, identifying material added, removed, and changed. We then summarized these differences and considered whether any of them met our criteria for serious postapproval risks.

The criteria we used for assessing label changes are specified for each section of the labeling and are shown in table 1.2. If any criterion was met, the drug was classified as having a serious postapproval risk. If all the labeling changes for a drug fell below the criteria, the changes were classified as nonserious. The criteria were developed after considerable discussion with FDA officials and examination of the types of changes made in the labeling for the drugs. Generally, labeling changes assessed in our analyses were intended to correspond to additional risks reflecting previously unsuspected adverse reactions identified in postmarketing surveillance. In addition, wording changes and changes adding information from preapproval testing were assessed in our label analyses if they represented a new appreciation of the risks of previously known adverse reactions. After we determined whether any labeling changes for a drug corresponded to serious postapproval risks, we prepared a summary of all label changes for the drug, separating them into serious and nonserious. We added to this summary all adverse reactions identified on the MART reports, where these were not already reflected in label changes.

Table 1.2: Criteria for Label Changes Reflecting Serious Postapproval Risk

Section	Criterion
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 suggesting that use of the drug may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or to death;[a] the limitation on use must correspond to the indications for which the drug was originally approved
Contraindications	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 a substantial danger that may lead to hospitalization, increases in the length of hospitalization, or severe or permanent disability or death[b]
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, increases in the length of 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	No change identified as reflecting serious postapproval risk
Overdosage	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

[a]The addition of a new indication is not a criterion, even though the inclusion of a new patient population might bring with it major risks for that group.

[b]The addition of warnings for a new indication are not construed as a serious additional risk.

We then asked FDA officials to review our assessments and judge whether they thought our separation of the changes into the categories of serious and not serious postapproval risk was accurate. After obtaining comments from FDA, we revised some of our assessments and then requested a panel of outside experts to review our categorization of the reviewed drugs into those with serious and nonserious postapproval risks. (The experts are listed in appendix III.) After revising the assessments based on experts' comments, we again submitted the entire assessment to FDA as part of its review of the draft of this report. After considering FDA's comments, we made our final classification of drugs into those with serious and those with nonserious postapproval risks.

In appendix II, we present the final list of labeling changes reflecting serious postapproval risks; we omit other changes because of the volume of the information. In chapter 2, we summarize the labeling changes reflecting serious postapproval risks for each class of drugs and describe in general terms the nature of the label changes for nonserious risks. The data for serious and nonserious risks are then analyzed in chapter 2. This answers our first evaluation question, describing the occurrence of serious postapproval risks.

We entered the information on whether a drug had serious postapproval risks into a computerized data base along with the information on various attributes of the drugs (therapeutic class, drug type, and length of time for approval) as mentioned above. We then analyzed these data using logistic regression analysis and log-linear modeling to determine which attributes were most strongly associated with serious postapproval risks. This analysis answers the second evaluation question and is presented in chapter 3, with supporting information in appendix IV.

We conducted our review of the labeling changes during the period September 1988 to January 1989, and we made revisions to the data base and the assessments of the seriousness of the postapproval risks as this report was being prepared and reviewed. Our review was conducted in accordance with generally accepted government auditing standards.

Strengths and Limitations

Our report has several major strengths. The most important is that we have demonstrated a methodology for developing an overview of postapproval risks. This methodology shows how to (1) identify serious and nonserious postapproval risks, (2) summarize the risks by drug class and body system affected by the risk, and (3) compare the additional risks with those known at the time of approval. The methodology also

shows how summary information on postapproval risks can be analyzed statistically in relation to attributes of drugs and the review process to address policy-relevant issues. Using only a limited set of data, we were able to examine such issues as (1) the extent to which postapproval risks are associated with the therapeutic value of new drugs, (2) the extent to which postapproval risks are associated with whether the drugs are available for use with children, (3) the importance of postmarketing surveillance in identifying new risks and the length of time it takes for new risks to emerge and be communicated to physicians, and (4) the relationship between the length of time for approval and the emergence of serious postapproval risks.

There are several possibilities for extending the methodology we used. First, the assessment of postapproval risk was limited to whether postapproval risk was serious or not. We believe these assessments are accurate but think it may be feasible and useful to make finer-grained judgments—that is, to estimate the extent of seriousness. HHS's comments (see appendix V) suggest the utility of further categorizations of postapproval risks. We believe that such categorization would enhance the development of criteria for determining the need for more safety information before approval, assessing the postapproval risks of individual drugs, and ascertaining when a drug should be withdrawn from the market for safety reasons.

The statistical analyses presented in chapter 3 provide only an initial understanding of the factors underlying the occurrence of serious postapproval risks, but they raise specific issues that need immediate further investigation and they indicate that further insights about why these risks emerge are possible. Our findings about serious postapproval risks for drugs with toxicity problems and for use with children are not conclusive but suggest the need for further study. The finding that some drugs with serious postapproval risks did not appear on the MART list raises the issue of the system's completeness of coverage. The findings about the time lag between a drug's approval, the reporting of adverse reactions, and the subsequent changing of labels deserves further attention; it is important that physicians be informed of additional risks as soon as possible. The finding that drugs with serious postapproval risks had had a shorter approval time than drugs without them deserves further attention; the results presented here raise the issue of the length of review.

The attributes examined here were not exhaustive. Time constraints and the difficulty in obtaining reliable data precluded our examining the

relationship between serious postapproval risks and such variables as characteristics of the firms developing the drugs, the route of administration of drugs, and the volume of use of the drugs.

Finally, our analysis did not include all the variables that may affect postapproval risk. Additional information in three areas is necessary to understand the source of serious risks: the inherent characteristics or uncertainties associated with the drugs themselves, the clinical testing they undergo, and the FDA review process. We plan to investigate these areas in a subsequent study.

The Occurrence of Serious Postapproval Risks

In this chapter, we answer the first evaluation question: What is the occurrence, overall, of serious postapproval risks? We first list the frequency of the drugs with and without these risks by the class of drug and overall. Next, we describe the types of changes in labeling that occurred during the study period (first identifying general nonserious changes and then by drug class, identifying the label changes that reflect the serious postapproval risks).

After describing the labeling changes and serious postapproval risks for each class, we examine the commonality, across all classes, of the medical effects that underlie the risks. In this regard, we discuss the issue of comparing the risks for one drug with those of another. Finally, we examine several issues relevant to providing a context for interpreting the findings.

The Additional Risks

We determined that 51.5 percent (102) of the 198 drugs we analyzed had serious postapproval risks, as evidenced by labeling changes or withdrawal from the market. All but 6 of these drugs were currently marketed as of September 1989 and thus were deemed by FDA to have benefits that outweigh their risks. Table 2.1 shows the breakdown by therapeutic class between drugs with no serious postapproval risks and drugs with such risks.[1] In appendix II, we list all the drugs in all classes and indicate whether or not they had serious postapproval risks; for those with serious postapproval risks, we identify the specific labeling changes and medically adverse effects that met our criteria. The postapproval risks for each class are summarized later in this chapter.

[1]This is FDA's classification and is based on the pharmacologic effect of drugs. Drugs in the same class are reviewed by a single division of FDA, using principles that are specific to that class.

Table 2.1: Drugs With and Without Serious Postapproval Risks 1976-85

Drug class	Total	Serious postapproval risk	
		No	Yes
101 Cardiac (I)	**17**	5	12
102 Antihypertensive-renal	**15**	9	6
201 Neurology	**5**	4	1
202 Psychopharmacological	**15**	6	9
203 Drug abuse	**5**	2	3
301 Fertility-antifertility	**5**	2	3
302 Metabolic-endocrine (I)	**9**	7	2
303 Metabolic-endocrine (II)	**8**	3	5
401 Antibiotic-systemic	**25**	7	18
402 Dermatologic	**13**	7	6
403 Anti-infective	**6**	4	2
404 Ophthalmic	**6**	3	3
405 Antiparasitic	**4**	2	2
501 Oncology	**9**	4	5
502 Radiopharmaceutical	**16**	11	5
503 Anti-inflammatory	**14**	3	11
601 Respiratory	**5**	5	0
602 Surgical	**2**	0	2
604 Anesthesia	**5**	2	3
605 Renal	**0**	0	0
801 Cardiac (II)	**1**	1	0
803 Gastrointestinal	**13**	9	4
Total	**198**	**96**	**102**

As shown in the table, the number of drugs analyzed by class during the 10-year period from 1976 to 1985 was generally rather small. For the smaller classes (for example, the 14 classes with fewer than 10 drugs), no conclusion about the class should be drawn regarding the relative prevalence of drugs with serious postapproval risks. As can be seen in the table, for the larger classes, the cardiac, anti-inflammatory, psychopharmacologic, dermatologic, and antibiotic drugs stand out as having had serious postapproval risks, while the antihypertensive-renal, radiopharmaceutical, and gastrointestinal drugs did not have serious postapproval risks. Overall, half or more of the drugs in 12 of the 22 classes had serious postapproval risks, while only 4 of the classes had fewer than a quarter of the drugs with such risks.

Table 2.2 presents the sources of information used to identify the drugs with serious postapproval risks. The first column shows the total

number of drugs approved in the period January 1, 1976, to December 31, 1985; the second column shows the number of drugs we reviewed for serious postapproval risks. Reasons for not analyzing the 11 drugs indicated are described in the previous chapter. The remaining columns show the total number of drugs with serious postapproval risks and how many were identified with the three principal criteria listed in the previous chapter.

Table 2.2: Sources of Information of Serious Postapproval Risks 1976-85[a]

				Source of information		
Drug class	Total approved	Total analyzed	Serious risks	Safety withdrawal	FDA drug bulletin	Label[b]
101 Cardiac (I)	18	17	12	0	1	12
102 Antihypertensive-renal	16	15	6	1	2	6
201 Neurology	5	5	1	0	1	1
202 Psychopharmacological	15	15	9	1	2	9
203 Drug abuse	5	5	3	0	0	3
301 Fertility-antifertility	5	5	3	0	1	3
302 Metabolic-endocrine (I)	9	9	2	0	2	2
303 Metabolic-endocrine (II)	9	8	5	1	1	4
401 Antibiotic-systemic	26	25	18	0	1	18
402 Dermatologic	14	13	6	0	1	6
403 Anti-infective	6	6	2	0	1	2
404 Ophthalmic	6	6	3	0	1	3
405 Antiparasitic	4	4	2	0	1	2
501 Oncology	9	9	5	0	0	5
502 Radiopharmaceutical	20	16	5	0	0	5
503 Anti-inflammatory	14	14	11	3	3	11
601 Respiratory	5	5	0	0	1	0
602 Surgical	2	2	2	0	2	2
604 Anesthesia	6	5	3	0	0	3
605 Renal	1	0	0	0	0	0
801 Cardiac (II)	1	1	0	0	0	0
803 Gastrointestinal	13	13	4	0	0	4
Total	**209**	**198**	**102**	**6**	**21**	**102**

[a]The number of drugs identified as having serious postapproval risks from withdrawal for safety reasons, the FDA Drug Bulletin, and a comparison of the original and most recent labels is sometimes more than the total number identified as having serious risks because information for a particular drug may have come from more than one source.

[b]Eight drugs were identified as having serious postapproval risks based only on MART reports in the following classes: antihypertensive-renal (alprostadil), metabolic-endocrine (I) (glipizide, glyburide), antibiotic-systemic (cefoperazone sodium, ceftriaxone sodium, cefotetan disodium, amoxicillin-potassium clavulanate), and anti-infective (acyclovir).

As the table shows, most of the information used to categorize a drug with respect to postapproval risk came from the labels. In general, FDA reports only the most serious postapproval risks in the FDA Drug Bulletin; these usually reflect label changes that have been made. However, in a few cases, the postapproval risks led to withdrawal of drugs before the label changes corresponding to the risks were made. Only one drug that was identified using the FDA Drug Bulletin was not considered to have serious postapproval risks; all others identified from this source were also identified by either label changes or withdrawal from the market.

To provide an overall perspective on the changes in labeling, we begin by examining the general changes observed since 1976. We then examine the labeling changes and serious postapproval risks for each class, particularly indicating the principal types of drugs in the class and any general types of changes and postapproval risks common to several drugs in the class.

Overview of Label Changes

Drug labels may be changed either to communicate new information or to communicate information more effectively. In our search for label changes that reflected the discovery of serious postapproval risk, we eliminated instances in which the aim was solely to communicate more effectively, and we eliminated some instances in which new information was presented.

Although the most extensive changes in labels occurred for drugs approved before 1980, most of those changes and some of the later ones were improvements in presentation, style, and wording of labels with little new information. Such instances did not, of course, reflect new risks in the use of the drugs.

A gradual trend to greater standardization was accelerated when FDA promulgated new labeling guidelines in 1979. While the guidelines did not change the major headings in the label (as described in chapter 1), they did provide more consistent direction on the types of information that should be included. For example, the information to be given under clinical pharmacology was more clearly distinguished from that required for the indications and usage sections. Thus, one of the major effects of these guidelines (observed in comparing labels before and after 1979) was that material moved from one section to another. Changes for the sake of standardization were not of interest in our study.

The 1979 guidelines also required the inclusion of certain new types of information, primarily in the description and precautions sections. For many drugs, these requirements led to the addition of inactive ingredients of tablet formulations. Again, such changes were not of interest in our study.

Some new information required by the guidelines did lead to the identification of serious risk not previously included in a label. For example, after 1979, the precautions section was required to contain information on carcinogenesis; mutagenesis; impairment of fertility; use by pregnant women, nursing mothers, and children; and the use of the drug in labor and delivery. Sometimes information was moved to the precautions section from other sections but in many cases new information was added to the label. When the new information described a serious risk not previously presented on the drug's label, we treated the case as one with serious postapproval risk.

Many changes in the labels occurred as a result of the addition of new indications for a drug. A company frequently submits a new drug application for a limited set of indications in order to get the drug approved and into the market while it is still carrying out clinical investigation trials to determine other, perhaps more important, uses for the drug.[2] With some drugs, rather extensive changes may be made to the clinical pharmacology section (to capture the pharmacokinetics in this new use) and the dosage and administration section (to reflect the appropriate method of treatment for the new indication). Less frequently, substantial changes are made in the contraindications, warnings, precautions, and adverse reactions sections. We excluded label changes associated with new indications because they arise from new uses of the drugs, not from better understanding of the risks involved in the original uses.

Some label changes arise from changes in the state of medical practice with respect to the treatment of a particular disease or the use of a particular drug class. Neither of these topics is static; rather, both are in a continual state of flux as knowledge is gained. As a result, information about newer members of a drug class can benefit from the experience with earlier approved drugs. The effect on labels is that some changes may reflect revised practices or increased understanding of a drug class. This may be reflected by additions to labels of the earlier drugs in a class of warnings, precautions, or adverse reactions similar to those

[2]Once a drug has been approved for marketing, a physician may prescribe it for any indication, even if the drug has not been approved for that use.

included on labels for newer drugs. In some cases, we judged these additions to constitute serious postapproval risks for an individual drug; it is important to distinguish these changes from those made as a result of adverse drug reactions observed after approval. In the discussion of changes for each class summarized below, we specifically identify this type of serious postapproval risk as "class labeling" changes. Some "class labeling" changes were not considered to be serious postapproval risks.

Finally, of most interest in our study are the label changes that correspond to risks not identified at the time of approval. As mentioned before, these risks arise primarily from adverse drug reaction reports and continued research on a drug. Resulting label changes range from minimal, such as the addition of a minor disease to the adverse reactions section, to increasingly extensive, with progressively more significant revisions in the precautions section, the warnings section, and the contraindications section.

Specific Risks by Drug Class

In this section, we describe in general terms the additional risks for each drug class (following the order in tables 2.1 and 2.2). Within each class, we note their relative seriousness and identify any changes that occurred across the class. We identify the particular adverse reactions that were observed. Each such reaction included here was conclusively linked to a specific drug and was manifested by a significant change in incidence, or by prolongation of hospitalization, severe or permanent disability, or death. Each of these adverse reactions resulted in additions to the adverse reactions section of the label and usually prominent changes (in boxed, bold, italic, or uppercase print) in the warnings, precautions, and other sections of the label as appropriate. Appendix II contains detailed information concerning the serious postapproval risks we identified for each individual drug.

Cardiac Drugs (I)

The new chemical entities approved in the cardiac (I) class included vasodilators, calcium channel blockers, antiarrhythmics, beta blockers, and nonglycoside inotropic agents; 12 of the 17 drugs analyzed in this class had serious postapproval risks. Many of these drugs have had changes in the warnings section for myocardial infarction or similar effects, including congestive heart failure, ventricular arrhythmias, atrial flutter or fibrillation, negative inotropic effects, or excessive conduction prolongation. Four of the 12 drugs with serious label changes had changes contraindicating or warning against the use of the drug in certain patients' groups because of possible myocardial infarction

(nifedipine and diltiazem), ventricular fibrillation (verapamil and disopyramide), congestive heart failure (disopyramide), and severe hypotension (verapamil and disopyramide). Four other drugs (tocainide hydrochloride, flecainide acetate, metaprolol tartrate, and atenolol) had additional warnings about the possibility of myocardial infarction. For the latter two, these warnings were added to boxed warnings concerned with abrupt cessation of therapy, particularly in patients with coronary artery disease; heightened attention was given to these warnings because of the addition of angina pectoris to the indications, which were previously limited to hypertension. We viewed these label changes as serious, despite our general rule that we did not consider label changes associated with new indications, because these warnings about myocardial infarction are also applicable to patients being treated for hypertension. For some of the drugs (verapamil, diltiazem, and disopyramide), various serious adverse effects arising from interactions with concomitantly used drugs were identified as serious label changes.

Another change reflected in many labels is the addition of hypersensitivity reactions (anaphylactoid reactions, erythema multiforme, and Stevens-Johnson syndrome). One or more of these reactions occurs at the serious level in the labeling of three drugs (nifedipine, verapamil, and amrinone lactate, although the latter results from the presence of sulfites).

Another change, for tocainide hydrochloride, involved boxing a previously included warning for blood dyscrasias, adding possible septicemia and shock, with fatalities occurring in 25 percent of reported agranulocytosis cases, and a change in the indications section recommending other alternatives in less serious arrhythmias because of the potential for serious hematologic disorders.

A final serious label change was the addition of an uppercase precaution for amiodarone hydrochloride about the possibility of breakthrough arrhythmia or aggravation possibly caused by hyperthyroidism and requiring aggressive medical treatment that could continue for months because of the delayed response to the drug and to any treatment of the hyperthyroidism.

Two drugs (nadolol and pindolol) were included among those with serious label changes because of recommended dose reductions.

Antihypertensive and Renal Drugs

Antihypertensive and renal drugs include angiotensin-converting enzyme inhibitors, agents used in hypotension and shock, diuretics and

renal tubule inhibitors, prostaglandin vasodilators, and agents for treating renal disease. Six of the 15 drugs analyzed in this class had serious postapproval risks. There was no systematic change in the labeling for these drugs. The most serious postapproval risk occurred for the drug ticrynafen, which was withdrawn from the market because of severe, possibly fatal, hepatic injury. For enalapril maleate, several warnings and precautions were added to the label in connection with the possibility of myocardial infarction, cerebrovascular accident, renal failure, blood dyscrasia, pancreatitis, and hypersensitivity effects as adverse reactions, and additional high-risk groups were identified as having possibly fatal reactions. For captopril, warnings about neutropenia and agranulocytosis were considerably expanded, identifying a fatality rate of 13 percent in patients with particular serious illnesses.

In the case of minoxidil, a warning was added for ischemia of special sense organs, particularly a decrease or loss of hearing or vision in certain patients. For alprostadil, the serious label change was the addition of convulsions to the adverse reactions section. Finally, for dobutamine hydrochloride, the label change was the addition of a warning about anaphylactic and life-threatening or less severe asthmatic episodes resulting from the inactive ingredient sodium bisulfite.

Neurology Drugs

Neurology drugs include muscle relaxants, anticonvulsants, and antiemetics. One of the five drugs in this class had serious postapproval risks. The primary serious postapproval risk for this drug, valproic acid, concerned hepatic failure resulting in fatalities, particularly for specific categories of children younger than 2 years of age, possibly preceded by nonspecific disorders with normal serum biochemistry and with the possibility that hepatic dysfunction may progress even when the drug is discontinued. There were also warnings added about teratogenic neural tube defects (spina bifida), severe central nervous system depression when used with phenobarbital, and breakthrough seizures when used with phenytoin.

Psychopharmacological Drugs

Psychopharmacological drugs include antidepressants, antipsychotics, antianxiety agents, and sedatives and hypnotics. Nine of the 15 drugs in this class had serious postapproval risks. Similar warnings were added to the labels of several drugs in this class for three related types of risk: neuroleptic malignant syndrome and tardive dyskinesia, seizures or convulsions, and withdrawal seizures. Frequently, warnings for these risks are identical for the different drugs and hence may be considered class labeling—that is, labeling used even in the absence of reports of the specific adverse reaction for the particular drug.

The label changes for midazolam hydrochloride included a warning about convulsions (even at the recommended dosages) but, more importantly, about possible respiratory depression and arrest resulting in death or hypoxic encephalography, arising primarily in connection with dosage and administration (with recommendations for dosage individualizations, avoidance of bolus injections, slow administration, and continuous evaluation of the sedative effects being achieved). The drug nomifensine maleate was withdrawn from the market because of significant morbidity and fatal cases from immune-mediated injury, hemolytic anemia, and hepatic disorders with potentially life-threatening sequelae leading to acute renal failure.

The label change reflecting serious postapproval risk for trazodone hydrochloride was the addition of an uppercase warning of an association between the drug and the occurrence of priapism, requiring surgical intervention in one third of the cases with permanent impairment of erectile function or impotence in a portion of these cases. For two drugs, amoxapine and pimozide, warnings were added for additional risks of neuroleptic malignant syndrome, tardive dyskinesia, and renal failure. In addition to midazolam hydrochloride, four other drugs (amoxapine, maprotiline hydrochloride, bupropion hydrochloride, and triazolam) had label changes warning about convulsions and seizures associated with use at the recommended dosages. Finally, two drugs, maprotiline hydrochloride and alprazolam, had warnings added for the serious risks of withdrawal seizures associated with rapid decrease or abrupt discontinuation of the drug.

Drug Abuse Drugs

Drug abuse drugs include narcotic analgesics, narcotic antagonists, and nicotine substitutes. Three of the five drugs approved in this class had serious postapproval risks, all concerned with the possibility of seizures arising from respiratory depression associated with the drugs. The most serious changes were for buprenorphine hydrochloride, for which several warnings and cautions were added to the labeling, the most prominent being the addition that clinically significant respiratory depression could occur with the recommended dose range. For butorphanol tartrate and nalbuphine hydrochloride, the possibility of respiratory depression had been recognized, but the labeling changes heightened the concern and precautions associated with respiratory depression occurring from use of the drugs.

Fertility and Antifertility Drugs

Fertility and antifertility drugs include androgens, estrogens, and uterine-acting products. Three of the five drugs in this class had serious postapproval risks. The most extensive changes occurred for ritodrine

hydrochloride, including increased concern in the boxed warning for fluid overload resulting in maternal pulmonary edema, possibly leading to myocardial ischemia, myocardial necrosis, arrhythmias, premature atrial and ventricular contractions, ventricular tachycardia, and bundle branch block, and also with the addition of a warning for sulfite-caused allergic type reactions, including anaphylactic symptoms and life-threatening asthmatic episodes.

The label changes for dinoprostone included the addition of a contraindication for patients with active cardiac, pulmonary, renal, or hepatic disease and the addition to the boxed warning that all patients, not just those having abortions, should be treated under emergency conditions in hospitals. The changes for danazol included putting into bold print the warning about use in pregnancy (recommending the use of a nonhormonal method of contraception) and the addition of a bold print warning about possible androgenic effects (clitoral hypertrophy and labial fusion) in the fetus.

Metabolic and Endocrine Drugs (I)

Metabolic and endocrine drugs include adrenal-ACTH agents, drugs for bone calcium-phosphorus metabolism, growth hormones, oral hypoglycemic agents, amino acid nutrients, and vasopressin. Two of the nine drugs in this class had serious postapproval risks. The labeling change for both drugs (glyburide and glipizide) is the addition of several severe adverse skin reactions (including exfoliative dermatitis, Stevens-Johnson syndrome, and epidermal necrolysis).

Metabolic and Endocrine Drugs (II)

Metabolic and endocrine drugs include dopamine agonists, gonadotropins, growth hormone, insulins, lipid altering agents, and thyroid drugs. Five of the eight drugs analyzed in this class had serious postapproval risks. For probucol, the label changes included the addition that the drug is contraindicated in patients with certain preexisting heart conditions (myocardial infarction, serious ventricular arrhythmias, and syncope of cardiovascular origin) because of the possibility of serious arrhythmias. The label changes for bromocriptine included the addition that the drug is contraindicated in cases of uncontrolled hypertension, because of the possibility of hypertension with seizures, stroke, visual disturbances, and acute myocardial infarction. For protirelin, the warning about marked changes in blood pressure, with possibly severe degrees of hypotension or hypertension, was made more emphatic by putting it into uppercase print. For gemfibrozil, there was an increase in the triglyceride level used as the criterion for treatment and additional warnings about increased mortality, acute renal failure, myositis, hematologic changes, and other adverse effects. The drug somatotropin was

withdrawn from the market because of the possible contamination of the product with Creutzfeldt-Jakob disease.

Antibiotics

Antibiotics include penicillins, cephalosporins, aminoglycosides, and other antibiotics and had serious postapproval risks noted in 18 of 25 drugs analyzed. The increased risk for amikacin sulfate was the addition to the boxed warning that safety beyond 14 days was not established (in connection with potential neurotoxicity when used for longer than recommended) and warning about neuromuscular blockade and respiratory paralysis and the addition to the precautions section of the possibility of irreversible deafness, renal failure, and death due to neuromuscular blockade when used topically in association with surgical procedures. Several warnings and precautions were added to the label for the drug netilmicin sulfate, including hypersensitivity reactions, muscular weakness, and peripheral neuropathy or encephalopathy. Seven drugs had label changes because the drug was implicated in acute renal failure, interstitial nephritis, or seizures in patients with existing renal impairment.

The most frequent postapproval risk noted in this class (for nine drugs) was the addition of a warning for pseudomembranous colitis. This may be viewed as class labeling, since the wording is the same in the labels of several of these drugs. A warning about severe hypersensitivity reactions was added to the labeling for six drugs in this class, and six others in this class had warnings about severe blood disorders added to their labels.

Dermatologic Drugs

Dermatologic drugs include fungicides, antipruritics, medicated detergents and shampoos, steroidal skin products, and nonsteroidal anti-inflammatory skin products. Six of the 13 drugs analyzed in this class had serious postapproval risks. The most extensive label changes occurred for isotretinoin, including the addition of a boxed contraindication (against use by pregnant women or those who intend to become pregnant, because of major fetal abnormalities), the addition of a boxed warning about the occurrence of pseudotumor cerebri, and reductions in the recommended dosages.

Three of the drugs (desoximetasone, diflorasone diacetate, and amcinonide) had "class labeling" changes—namely, a warning about hypothalamic-pituitary-adrenal axis suppression and Cushing's syndrome, particularly in pediatric use, and hyperglycemia and glucosuria in some patients. The risks for the 2 other drugs pertain not to the drug itself but to other components of the drug. For meclocycline sulfosalicylate,

there is an additional warning for sulfite sensitivity with possible anaphylactic symptoms and life-threatening or less severe asthmatic episodes. For malathion, concern about the flammability of the product from open flame, hair dryers, electric heat, or smoking was put into the boxed warning.

Anti-Infective Drugs

The drugs in the anti-infective class include systemic antiviral agents, drugs for urinary tract infections, antiparasitic agents, and antifungal agents. Two of the six drugs in this class had serious postapproval risks. For ketoconazole, a boxed warning was added for additional risks from fatal hepatotoxicity (along with other forms of liver dysfunction) and a bold warning was added for anaphylaxis occurring on the first dose. For acyclovir, acute kidney failure, polyneuritis, and agranulocytosis were added to the adverse reactions section.

Ophthalmic Drugs

Ophthalmic drugs include ophthalmic antibiotics, ophthalmic adrenergic agents, and other ophthalmic agents. Three of the six drugs in this class had serious postapproval risks. The additional risks for two of these drugs, timolol maleate and levobunolol hydrochloride, arise from their beta-adrenergic properties and correspond to adverse effects seen with such drugs administered systemically rather than as eye drops. The observance of these effects led to the addition of a contraindication for patients with a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, atrioventricular block, overt cardiac failure, or cardiogenic shock and the addition of warnings about severe respiratory reactions, cardiac reactions, and deaths in association with bronchospasm and cardiac failure. For sodium fluorescein, there was additional concern about shock, convulsions, acute myocardial infarction, and other signs and symptoms of hypersensitivity, which in rare cases have resulted in death.

Antiparasitic Drugs

The drugs in the antiparasitic class include antimalarial, antihelmintic, and antischistosomal agents. Two of the four drugs in this class had serious postapproval risks. A boxed warning was added for the drug combination sulfadoxine and pyrimethamine about fatalities from severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hepatocellular necrosis, with contraindications for prophylactic use in patients with severe renal insufficiency, marked liver damage, or blood dyscrasias and with additional qualifications for use only in circumstances in which there was chloroquinine resistance. For praziquantel, a contraindication was added that ocular cysticercosis should not be treated because parasite destruction within the eye may cause irreparable lesions.

Oncology Drugs

Oncology drugs include general oncologic agents, cytotoxic alkylating agents, and antineoplastic agents. Five of the nine drugs in this class had serious postapproval risks. The label changes for cyclosporine included the addition of a concern about a syndrome of thrombocytopenia and microangiopathic hemolytic anemia, significant hyperkalemia and hyperuricemia, and convulsions and the addition of a bold print warning about anaphylactic reactions requiring continuous observation immediately following the beginning of infusion and at frequent intervals thereafter. Two drugs, carmustine and lomustine, had label changes warning about dose-related pulmonary toxicity characterized by pulmonary infiltrates or fibrosis and dose-related bone-marrow dysplasia and toxicity (including acute leukemia), where the cumulative dose over a series of treatments (about 6 months) is the critical variable. These drugs also had additional risks for secondary malignancies associated with long-term use and the possibility of fetal harm if the patient should become pregnant.

The additional postapproval risks for cisplatin included the addition of severe irreversible neuropathies when dosage is exceeded and vascular toxicities when the drug is used with other antineoplastic agents, with possible myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, or cerebral arteritis. Finally, for tamoxifen citrate, the label changes consisted of warnings about oncogenic activity during pregnancy (including spontaneous abortions, birth defects, and fetal deaths) and ocular changes (the latter even at recommended doses).

Radiopharmaceutical Drugs

Radiopharmaceutical drugs are a class that includes radioactive diagnostic agents and radio-opaque contrast agents. Five of 16 drugs analyzed in this class had serious postapproval risks. For 4 radiopharmaceuticals—iopamidol, iohexol, metrizamide, and the combination ioxaglate meglumine and ioxaglate sodium—warnings were added to the label about the possibility of convulsions and seizures and, for the last drug mentioned, the possibility of aggravating a preexisting myocardial infarction. The labeling change for gallium citrate Ga-67 was related not to the drug itself but to the use of benzyl alcohol as a preservative, which may cause a potentially fatal "gasping syndrome" in infants.

Anti-Inflammatory Drugs

Anti-inflammatory drugs include general anti-inflammatory agents, inhalation corticosteroids, and nonsteroidal anti-inflammatory drugs. Eleven of the 14 drugs in this class had serious postapproval risks; all are nonsteroidal anti-inflammatory drugs. The risks for this class are highly similar; frequently the same wording appears on the labels of

several drugs. The risks are generally associated with four types of adverse reactions: gastrointestinal bleeding, acute interstitial nephritis, severe hepatic reactions, and hypersensitivity reactions. Three of these drugs were withdrawn from the market because of serious postapproval risks in these categories: suprofen, because of concern about flank pain; benoxaprofen, because of deaths from liver damage (also had serious label change for kidney damage); and zomepirac sodium, because of a suspected greater-than-acceptable risk of anaphylactic reactions.

It can be argued that the drugs in this class have virtually the same risks and that label changes do not represent additional risks but, rather, are routine changes made when a particular adverse reaction is observed after approval. It is argued that several of the adverse reactions will not be observed because of the inherently small populations examined during clinical testing; it is claimed that the original label recognizes the possibility that such adverse reactions will emerge after approval. We have taken the position that label changes reflect serious postapproval risks if the change corresponds to actual fatalities not previously mentioned.

Seven drugs in this class (piroxicam, fenoprofen calcium, naproxen, diflunisal, tolmetin sodium, meclofenamate sodium, and sulindac) had label changes that added warnings reflecting serious postapproval risks for renal failure. Warnings about hypersensitivity reactions were added to the labels for four drugs (meclofenamate sodium, sulindac, piroxicam, and diflunisal). Five drugs (naproxen, fenoprofen calcium, tolmetin sodium, sulindac, and piroxicam) had additional warnings for hepatic failure. Four drugs (fenoprofen calcium, sulindac, piroxicam, and diflunisal) had serious additional warnings about gastrointestinal bleeding. Three drugs (piroxicam, naproxen, and diflunisal) had additional warnings about drug interactions. Finally, one drug (auranofin) had serious label changes corresponding to hematologic reactions, including aplastic anemia and other blood disorders.

Respiratory Drugs

Respiratory drugs include bronchodilators, $beta_2$ agonists, and oral antihistamines. None of the five drugs approved in this class had serious additional risks.

Surgical Drugs

Surgical drugs include caloric supplements and injectable enzymes. Both drugs in this class had serious postapproval risks. For the drug chymopapain, there was a considerable expansion of the boxed warning reflecting a better understanding of the conditions potentially contributing to anaphylactic reactions, leading to several recommendations about

use: against concomitant discography and injection in more than one disc, the necessity of an open intravenous line in place for possible treatment of anaphylaxis, and that chemonucleolysis not be performed if adequate imaging X-ray equipment were not available to ensure proper needle placement. For the other drug, intravenous fat emulsion, a boxed warning was added to the label because of the risk of fat overloading, which could result in several dangerous conditions, including reported deaths in preterm infants.

Anesthesia Drugs

Anesthesia drugs include local anesthetics, neuromuscular blocking agents, general anesthetics, and narcotic anesthetic adjuncts. Three of the five drugs analyzed in this class had serious postapproval risks. For etidocaine hydrochloride, there were several additional warnings, including the addition of an uppercase warning about the necessity of resuscitative equipment because delay might result in toxicity, underventilation, acidosis, cardiac arrest, and death, and the addition of warnings about use in labor and delivery (paracervical block) with possible maternal, fetal, and neonate toxicity involving the central nervous system.

Atracurium besylate had label changes warning about risks of anaphylactoid reactions and the "gasping syndrome" in neonates because of the preservative benzyl alcohol. For etomidate, the serious label changes warned against the possibility of cortisol and aldosterone suppression from prolonged infusion.

Renal Drugs

The one drug approved in this class is an agent for treating renal disease. The changes in its labeling were not analyzed, because we did not have suitable labels for comparison.

Cardiac Drugs (II)

The one cardiac (II) drug approved is a chelating agent. It did not have any serious postapproval risks.

Gastrointestinal Drugs

Gastrointestinal drugs include antimotility and antispasmodics, antiulcer agents, gastrointestinal diagnostic drugs, gallstone solvents, liver drugs, and motility stimulants. Four of the 13 drugs in this class had serious postapproval risks. For difenoxin hydrochloride with atropine sulfate, the principal label changes were the addition of an uppercase warning that overdosage could result in severe respiratory depression and coma, possibly leading to permanent brain damage or death, particularly in children younger than 2 years of age, and the conversion of several warnings to uppercase about keeping the drug out of reach of children.

For cimetidine, the serious label changes include cardiac arrhythmias and hypotension following rapid administration by intravenous bolus, confusional states predominantly in severely ill patients, and drug interactions for several drugs with effects from reduction in hepatic metabolism. For lactulose, the serious label change was the addition of a warning about potential explosive reaction from accumulation of H_2 gas in patients who may undergo electrocautery procedures during proctoscopy or colonoscopy. For metoclopramide, warnings and adverse reactions were added for depression, extrapyramidal symptoms, and tardive dyskinesia (the latter potentially irreversible with increasing duration and total cumulative dose).

Aggregate Analysis of Additional Risks

In this section, we aggregate the postapproval risks detailed above to show how this information may be useful in the review process or in postmarketing surveillance. First, we classify these adverse effects into categories of drug-induced disease and describe how the postapproval risks observed in this study fit into this classification.[3] Next, we consider how the postapproval risks compare to risks known at the time of approval.

Drug-Induced Diseases

A way to achieve greater specificity about the degree of risk would be to classify the postapproval risks by drug-induced disease category. We observed that the same type of drug-induced disease may appear in several classes. For example, hypersensitivity reactions including anaphylactoid reactions, erythema multiforme, and Stevens-Johnson syndrome were added as serious postapproval risks for drugs in the following classes: antibiotics, cardiac drugs, antihypertensive drugs, anti-inflammatory drugs, anti-infective drugs, anesthesia drugs, antiparasitic drugs, and surgical drugs.

Therefore, we classified the postapproval risks for each drug according to the different categories of drug-induced diseases that were added to the labels of the various drugs.[4] They are

[3]We use the 1985 hierarchical arrangement of drug-induced disease categories developed by FDA for coding adverse drug reaction reports. These categories generally identify the body system affected by the drug.

[4]The categories used here are a subset of the FDA categories. We use only those that correspond to the serious postapproval risks identified in the label analyses.

- Cardiovascular system effects: heart failure, myocardial infarction, arrhythmias, hypotension, and hypertension;
- Pathological abnormalities: anaphylaxis, Stevens-Johnson syndrome, effects of drug interactions on plasma concentrations, and acute leukemia;
- Respiratory depression and arrest: pulmonary toxicity and edema, obstructive pulmonary disease, and bronchospasm;
- Central nervous system effects: depression of the central nervous system, convulsions, and seizures;
- Renal effects: renal failure, acute interstitial nephritis, nephrotic syndrome, hematuria, and proteinuria;
- Gastrointestinal effects: hepatotoxicity, cholestatic jaundice or hepatitis, pseudomembranous colitis, gastrointestinal bleeding, and perforated ulcers;
- Hematologic system effects: blood dyscrasias, bone marrow depression, agranulocytosis, leukopenia, thrombocytopenia, prothrombin decrease, hemolytic anemia, aplastic anemia, and hemorrhage;
- Fetal and developmental effects: teratogenic effects, birth defects, fetal toxicity and deaths, abortions, and developmental abnormalities; and
- Ophthalmic effects: loss or decrease of vision, cataracts, and visual disturbances.

The drugs included in this study differ in the number of categories of drug-induced diseases for which they had serious postapproval risks. No drug had additional risks that fell into more than five disease categories; approximately one quarter of the drugs had serious postapproval risks in three or more disease categories. There was considerable grouping of the serious postapproval risks by disease category and drug class.

Once adverse reactions are classified by type of disease, there are further opportunities to provide FDA reviewers with useful information. For example, reviewers should be better able to estimate the extent of risk for different kinds of patients if they have better knowledge of adverse reactions and disease types for drugs in the same class already on the market. This can be useful in both the review process and postmarketing surveillance.

Comparisons to Risks Known at Approval

When they are approved, many drugs have adverse reactions in nearly all disease categories; most of these are not serious. Some drugs have very few stated adverse effects, while others have a large number. Even though most drugs have had label changes since approval, seldom do the labeling changes correspond to a large increase in the number of adverse

reactions identified for a drug. The number of nonserious labeling changes is greater than the number of serious postapproval risks. Hence, the number of serious postapproval risks is small when compared to the number of adverse reactions that had been identified at the time of approval.

The risks may vary in the seriousness of the adverse reactions for a particular category of drug-induced disease. Within a given category, the risks may fall along a spectrum that includes other less severe adverse reactions. For example, hepatotoxicity is a gastrointestinal problem in which the observed effects range from small, transient, and reversible changes in liver function tests through jaundice and hepatitis to fatal cholestatic jaundice or hepatitis. Liver function abnormalities detected during clinical trials may be a predictor of the more serious liver diseases, which might only be observed when the marketed drug is used by a wider population. The possibility of relationships between serious postapproval risks and previously identified, less severe adverse reactions has been discussed in the literature (Tilson, 1986; Zbinden, 1987).

The pattern we observed—namely, that serious postapproval risks are frequently more serious manifestations of adverse effects known at the time of approval—can be used during the review process. In particular, more detailed analysis of this relationship can reveal the likelihood that more serious diseases will be observed. This information can be used to specify the need for more data during the review process or in postapproval research.

Agency Comments and Our Response

HHS criticized our criteria on the grounds that they allowed the inclusion of drugs as having serious postapproval risks that could not possibly be related to the drug review process, arguing that an examination of the specific process used for an individual drug cannot possibly be relevant to the likelihood that such events will be discovered after approval. HHS also stated that the draft report incorrectly portrays the drug review process as involving "trade-offs" controllable by FDA.

This is a misunderstanding. As already noted, our objective in this report was not to examine the drug review process and, hence, not to critique FDA's performance in that process. Instead, the effort was to search for the factors that are related to postapproval risks, regardless of their source, rather than to look for deficiencies in the review process.

Attributes of Drugs Associated With Serious Postapproval Risks

In this chapter, we address the question of whether certain attributes of drugs (including the drug review process) may be associated with postapproval risks. In our analysis, we include factors such as (1) the degree of therapeutic gain expected from the drug and various classification subtypes, (2) whether the drug appeared on FDA's MART list, and (3) the length of time for approval. As mentioned in the scoping section of chapter 1, we were guided by the availability of reliable data in this analysis.

In the discussions and tables presented in this chapter, we use logistic regression analysis and log-linear modeling to analyze the attributes for their association with serious postapproval risk.[1] We discuss only briefly factors that were not significantly related to serious postapproval risks. In this analysis, we consider the drugs simply from the standpoint of whether they did or did not have serious postapproval risks. We do not examine the degree of seriousness of risk. We first present a discussion of the variables we considered in our analysis, along with some hypotheses for their expected association. We then present the results of our analysis.

Variables Included in the Model

Table 3.1 summarizes the variables used in our analysis. The summary includes the mean or average and the standard deviation of the values for each of the variables. All variables except the length of time for approval have only two values, 0 and 1, with their meanings shown in the table. As a result, the mean for these variables is the same as the fraction of drugs for which the value is 1. Thus, 13 percent of the drugs were categorized by FDA as having important therapeutic gain, 37 percent were of modest therapeutic gain, 17 percent were marketed abroad before FDA approval, 29 percent of the drugs were reviewed for use in children, 42 percent appeared on FDA's MART list, 59 percent were approved between 1981 and 1985 (or conversely, 41 percent between 1976 and 1980), 23 percent were approved during December, and the average length of time for approval was 2.6 years (the maximum for one drug being 11.3 years).

[1] See also appendix IV for more detail on the log-linear modeling.

Table 3.1: Basic Variables in the Analysis[a]

Variable	Value	Mean	Standard deviation
Important therapeutic gain	0 = No, 1 = Yes	0.131	0.339
Modest therapeutic gain	0 = No, 1 = Yes	0.374	0.485
Foreign marketing experience	0 = No, 1 = Yes	0.167	0.374
Use with children	0 = No, 1 = Yes	0.288	0.454
Appearance on MART list	0 = No, 1 = Yes	0.419	0.495
Period of approval	0 = 1976-80, 1 = 1981-85	0.586	0.494
Month of approval	0 = Jan.-Nov., 1 = Dec.	0.232	0.423
Years taken for approval	Range from 0 to 11.3 years	2.555	1.862
Serious postapproval risk	0 = No, 1 = Yes	0.515	0.501

[a]Total number of drugs was 198.

The Therapeutic Gain of a Drug

FDA's classification of a drug by its therapeutic gain is an assessment of its expected role in dealing with particular diseases. A drug judged to be a so-called "important" therapeutic gain is expected to have a substantial medical benefit. At the same time, however, such a drug may represent a new chemical approach for dealing with particular diseases and, hence, may have fewer similarities with previous drugs and greater uncertainties about their risks. In other words, a drug could provide a substantial benefit and could also involve serious and unexpected risks.

There are differing views about how the degree of therapeutic gain might be related to postapproval risk. One view is that drugs rated as having important gains are likely to be substantially different from drugs already on the market. Being different, they are more likely to be scrutinized closely and therefore less likely to have serious postapproval risks than drugs similar to ones already available. A possible consequence of this hypothesis is that subsequent drugs of the same type are likely to receive less intense scrutiny during review and the adverse effects of these secondary drugs (those with "modest" or "little or no" therapeutic gain) are more likely to be overlooked. Another view is that the drugs that are substantially different are more likely to have unexpected adverse effects that will not be identified during the review process and hence are more likely to have serious postapproval risks. Because the therapeutic gain of a drug may be related to postapproval risk, we created two appropriate variables for our model: one indicates

whether a drug had an important therapeutic gain and the other indicates whether a drug had a modest therapeutic gain.[2]

Foreign Marketing, Use With Children, and Other Review Categories

FDA may assign a drug to one or more of seven "classification subtypes"; this classification may have some relationship to postapproval risks. These subtypes (and the number of drugs from our study in each subtype) are

- an orphan drug (7 drugs);
- a designated orphan drug (7 drugs);
- a drug already marketed overseas (33 drugs);
- a drug subject to unique conditions of approval (15 drugs);[3]
- a drug whose approval is considered sensitive (4 drugs);
- a drug that has important problems of toxicity (8 drugs);[4] and
- a drug reviewed for use with children (57 drugs).

Although it is possible to create variables representing each of these subtypes, we did so only for those marketed overseas and those for use with children.

Among the orphan and designated orphan drugs and the drugs considered sensitive, 3, none, and 2, respectively, had serious postapproval risks. Among the 8 drugs with important problems of toxicity, 7 had serious postapproval risks; the possibility that these toxicity problems could carry over to the postapproval phase seems plausible. Among the 15 drugs subject to unique conditions of approval, 11 had serious postapproval risks; however, all but 1 of these were anti-inflammatory drugs, and all but 1 of the 15 drugs with this classification were approved by one reviewing division of FDA. Because of the small numbers of drugs in these five drug subtypes, these variables were not included in our model.

The numbers of drugs classified as being reviewed for use with children or as having been marketed abroad are sufficiently large to include in our model. We included a variable indicating whether a drug was reviewed for use with children. We would expect that drugs for children

[2]We used two variables to represent therapeutic gain for technical reasons associated with the log-linear modeling. See appendix IV for the detailed explanation.

[3]For example, additional studies required by "approvable" or "approval" letter for the new drug application.

[4]The toxicity exceeds or is unique from the drugs already approved for the same patients.

would undergo a greater intensity of review before being approved and, hence, would have fewer serious postapproval risks. We also included a variable indicating whether a drug was marketed abroad before FDA's approval. For these drugs, we would similarly expect fewer serious postapproval risks, since these drugs would have had the benefit of postmarketing experience in foreign countries, which could then be used for a more informed FDA review.

Appearance on FDA's MART List

As mentioned earlier, FDA monitors certain drugs for which adverse reactions have been reported. A list of such drugs is published each month on the MART report. Because appearance on the MART list might in some cases be followed by a label change signaling a serious postapproval risk, we created a variable to see if there is indeed a relationship.

In addition, we could test the hypothesis that most serious additional risks surface within 3 years of approval. This is important for determining how quickly new risks are identified and communicated to physicians through label changes. We had decided to examine only drugs approved through the end of 1985, expecting that this cutoff would allow sufficient time for drugs approved near the end of the period to have had postmarketing surveillance that would have identified any substantial additional risks. We were also able to examine the variable for appearance on the MART list in conjunction with time variables described below.

Time Variables

Our drug data base included, for each drug, the date its application was submitted to FDA and the date the drug was approved. With this information, it was possible to construct several variables pertaining to time, permitting us to examine certain hypotheses that have been described in the literature and in discussions with FDA officials and other experts.

Period of Approval

First, we established a variable for period of approval, letting it have a value of 0 if approval was in the period 1976-80 and a value of 1 if in 1981-85. With this variable, we could look for an association between postapproval risks and the time period when drugs were approved. We could also examine the time lag between appearance on the MART list and labeling changes. Since the MART system was not established until late 1985, we would expect that fewer drugs approved between 1976 and 1980 with serious postapproval risks would have appeared on the list, the opposite being true for drugs approved between 1981 and 1985.

Month of Approval

The literature includes a hypothesis that drugs approved in the last month of the year may have more serious postapproval risks than drugs approved in other months. Specifically, it has been noted (Kaitin, Richard, and Lasagna, 1987; Public Citizen Health Research Group, 1988) that the number of drugs approved in December or the fourth quarter of the year is disproportionate to the number approved at other times, raising the possibility that end-of-the-year drugs may be rushed through the approval process. To test the possibility that drugs approved late in the year have greater postapproval risks, we created a variable for month of approval, letting it have a value of 0 if approval occurred in January through November and a value of 1 if approval occurred in December.

Length of Time for Approval

Finally, we calculated the difference between the submission date and the approval date to create a variable called length of time for approval. This variable allows us to examine the hypothesis that drugs with shorter approval times are more likely to have serious postapproval risks than drugs with longer approval times.

Results of Analysis

To determine whether and to what extent each of the eight variables shown in table 3.1 was related to the presence of serious postapproval risks, we performed several analyses. To measure the relationships, we used odds ratios.[5] First, we examined each of the variables by itself in comparison with serious postapproval risks. This analysis does not control for the interrelationships among the eight variables; in the second step, we used a logistic regression model, which allowed the direct effects of the variables to be estimated simultaneously. This analysis indicated that some of the variables were not statistically significant; in the third step of our analysis, we eliminated the insignificant terms from our model and examined the strength of relationship for the remaining variables.

The results of these analyses are presented in table 3.2. The first column presents the odds ratios for the bivariate analysis (that is, each variable examined by itself in relation to postapproval risk). This analysis indicates that drugs reviewed for use with children, those appearing on the MART list, and those approved between 1976 and 1980 had a statistically

[5]Also called relative risk, the odds ratio indicates how closely the variable of interest is associated with the variable for serious postapproval risk. The higher the odds ratio, the more likely that serious postapproval risk will occur; the lower the odds ratio, the less likely that serious postapproval risk will occur; if the odds ratio is 1.0, the two variables are considered to be independent. We accept the hypothesis that the estimate of relative risk could not have occurred by chance if the level of significance is lower than a stated probability.

significant increased likelihood of being identified as having serious postapproval risk. This first column represents "gross" estimates of the effects of the different variables; the second column presents the "net" effects when considering possible interactions among the variables. The same three variables were identified as statistically significant in the full model, indicating that none of the other variables have an important association either with serious postapproval risk or with any of the variables that do have an association. The third column presents the results of "reducing" the complexity of the full model by eliminating the insignificant variables and their effects (which otherwise introduce random variations in estimating the strength of the three significant variables). The "reduced" model can also be recast as a simple, log-linear model for examining the interactions among the three significant variables.

Table 3.2: Odds Ratios for Effects of Variables on Serious Postapproval Risk

Variable	Bivariate models	Full main effects model	Reduced main effects model
Important therapeutic gain	0.93	0.63	•
Modest therapeutic gain	1.08	0.62	•
Foreign marketing experience	1.34	0.78	•
Use with children	2.16**	2.07*	2.11**
On MART list	7.61***	11.86***	10.62***
Period of approval	1.62*	2.94***	2.85**
Month of approval	0.74	0.89	•
Length of time for approval	0.92	0.90	•

* $p < 0.10$.

** $p < 0.05$.

*** $p < 0.01$.

The purpose of log-linear modeling is to select the simplest model that adequately describes the interactions among the three independent variables and with postapproval risk, including only those that are statistically significant. The data that we wish to fit—that is, the four-way table in which postapproval risk is cross-classified by the variables use with children, appearance on the MART list, and period of approval—is portrayed in table 3.3. The simplest model that fits the data adequately and that cannot be significantly improved by the addition or substitution of another variable is the one in which postapproval risk is associated directly with each of the three other variables in the table. Each of these direct associations is significant, and no more complex interaction

among the variables is significant.[6] The expected frequencies and odds ratios computed using the preferred model are shown in table 3.4.

Table 3.3: Serious Postapproval Risks Compared With Use With Children, Appearance on MART List, and Period of Approval

Child use	MART list	Period	Serious postapproval risk: Yes	Serious postapproval risk: No	Total
Yes	Yes	1976–80	10	1	**11**
		1981–85	13	2	**15**
	No	1976–80	10	8	**18**
		1981–85	4	9	**13**
No	Yes	1976–80	14	1	**15**
		1981–85	28	14	**42**
	No	1976–80	14	24	**38**
		1981–85	9	37	**46**
Total			**102**	**96**	**198**

Table 3.4: Expected Frequencies, Odds, and Odds Ratios of Serious Postapproval Risks Compared With Use With Children, Appearance on MART List, and Period of Approval[a]

Child use	MART list	Period	Estimated serious postapproval risk: Yes	Estimated serious postapproval risk: No	Odds on risk	Odds ratios: Child yes: Child-no	Odds ratios: MART-yes: MART-no	Odds ratios: 1976-80: 1981-85
Yes	Yes	1976–80	10.26	0.74	13.90			
		1981–85	12.45	2.55	4.87			2.85
	No	1976–80	10.20	7.80	1.31		10.62	
		1981–85	4.09	8.91	0.46		10.62	2.85
No	Yes	1976–80	13.02	1.98	6.56	2.12		
		1981–85	29.28	12.72	2.30	2.12		2.85
	No	1976–80	14.52	23.48	0.62	2.12	10.62	
		1981–85	8.19	37.81	0.22	2.12	10.62	2.85
Total			**102**	**96**				

[a]Odds and odds ratio calculations are based on greater detail for the estimated serious postapproval risks.

The implications of selecting the preferred model are determined by using the odds and odds ratios presented in table 3.4. The highest odds on the presence of serious postapproval risks are for drugs approved for use with children, which appear on the MART list and were approved

[6]The preferred model, in this case known as the "main effects" model, has a chi-square value of 1.23 with four degrees of freedom. The small value assures us that the discrepancies between the expected frequencies under that model and the observed frequencies can reasonably be assumed to be due to chance. The expected frequencies in table 3.4 can be compared to observed frequencies in table 3.3. The process for selecting this model is described in appendix IV.

between 1976 and 1980. For this particular combination of categories, the odds on postapproval risks is 10.26/0.74, or 13.90. The lowest odds on serious postapproval risks is for drugs not approved for use with children, not on the MART list, and approved between 1981 and 1985; for this category, the odds on serious postapproval risks is only 8.19/37.81, or 0.22.

To understand the independent effects of the three variables on postapproval risks, we consider the odds ratios. To discern the effect of drugs for use with children, we would hold constant the appearance on the MART list and the period of approval and take the ratio of the odds that contrast those drugs that were so approved with those that were not. We would calculate 13.86/6.57 equals 2.12 for drugs that appeared on the MART list and were approved in the earlier period, 4.88/2.30 equals 2.12 for drugs that appeared on the MART list and were approved in the later period, and so on. An odds ratio of 2.12 appears in all cases, indicating that regardless of, or independent of, when they were approved, or whether they appeared on the MART list, drugs that were approved for use with children were more than twice as likely to involve serious postapproval risks as drugs that were not. Similar calculations lead to the findings that drugs appearing on the MART list are more than 10 times as likely to have serious postapproval risks as those that did not and that drugs approved between 1976 and 1980 are almost three times as likely to have serious postapproval risks as those approved between 1981 and 1985. In the next section, we consider the implications of these results, along with the finding of no significance for the other variables included in our analysis.

Interpretation of Results

Association With Attributes of Drugs

In this section, we consider the association of variables indicating therapeutic gain, foreign marketing experience, and review of a drug for children with the occurrence of serious postapproval risk. With respect to therapeutic gain, the results suggest that neither new kinds of drugs nor subsequent drugs of a class are likely to have more or fewer serious postapproval risks than other drugs. Overall, there is no association between the therapeutic gain of a drug and serious postapproval risk. Moreover, when the interaction of therapeutic gain with the length of

time for approval is considered, there is no significant association with serious postapproval risk.

The finding that drugs approved for use with children are more than twice as likely to have serious postapproval risks contradicts the hypothesis that such drugs were likely to have fewer serious postapproval risks. One possible explanation is that labeling changes for these drugs are more likely to be sensitive to additional risks for children. However, the fact that this class of drugs is more likely to have serious postapproval risks is troubling and needs further investigation, particularly in light of the discussion in the previous chapter suggesting that serious postapproval risks were independent of the existing profile of adverse reactions for the drug. This seems to indicate that the unknown risks at the time of FDA approval are particularly likely to affect children.

The analysis in table 3.2 shows that there is no significant association between drugs already marketed overseas and serious postapproval risks. This result is somewhat surprising because, as mentioned above, we would expect that foreign marketing experience would identify additional risks that would inform FDA approval. However, a requirement to report foreign marketing experience to the FDA began only in late 1985. Before then, foreign marketing experience did not have to be considered in FDA approval, and this might explain why such information did not show an effect in our study.

Association With Appearance on the MART List

As shown in table 3.2, there is a strong association between the presence of a drug on the MART list and the existence of serious postapproval risks for the drug. The odds that a drug will show serious postapproval risks are 7 to 11 times higher if the drug appeared on the MART list than if it did not. The strength of this association is perhaps not surprising, since appearance on the MART list should be a precursor to a label change that reflects serious postapproval risk.

Several additional insights about appearance on the MART list can be made by further examination of the data. A large number of drugs (37) with postapproval risks did not appear on the MART list, and a somewhat smaller number (18) that appeared on the MART list were judged not to have had serious postapproval risks. The latter situation is more easily explained. A drug is put onto the MART list if there is a suspicion from an adverse reaction report that the drug may have a previously unidentified risk. Inclusion on the MART list heightens FDA's awareness of reports

concerning the drug. If additional adverse reactions lead to the substantiation of previously unlabeled adverse reactions, a label change ensues. Thus, appearance on the MART list does not always mean the identification of a serious postapproval risk. This could be because either the relationship between the adverse reaction and the drug was not substantiated or the adverse reaction was not considered serious.

The log-linear results do not directly address the hypothesis that most serious postapproval risks surface within 2 or 3 years of approval. Additional detail is presented in table 3.5, which shows the breakdown for drugs with serious postapproval risks of appearance on the MART list and period of approval. The results support this hypothesis, showing that 50 percent of the drugs (24 of 48) in the earlier period (when there was no MART list) compared with more than 75 percent (41 of 54) for the later period had serious postapproval risks and also appeared on the MART list. In other words, drugs with serious postapproval risks approved in the late period were more likely to have appeared on the MART list.

Table 3.5: Appearance on MART Compared With Period of Approval for Drugs With Serious Postapproval Risks

	Mart list		
Period of approval	No	Yes	Total
1976-80	24	24	**48**
1981-85	13	41	**54**
Total	**37**	**65**	**102**

Table 3.5 provides some additional insights that we did not expect. We would have expected an even smaller percentage of drugs with serious postapproval risks from the earlier period to appear on the MART list if most of these additional risks occurred within 2 or 3 years. The high percentage (50 percent, or 24 of 48) indicates the possibility that new, serious risks may appear more than 5 years after approval. In addition, the table shows that 13 drugs approved between 1981 and 1985 and with serious postapproval risks did not appear on the MART list. We would expect this number to be zero if the MART list is capturing all serious adverse reactions in postmarketing surveillance. Some drugs approved in 1984 and 1985 with serious postapproval risks did not appear on the MART list. A better understanding of when knowledge of the risks stabilizes and why some drugs with serious risks do not appear on the MART list depends on when action was taken that led to our rating of serious postapproval risk; we did not develop this information.

Another aspect of the relationship between appearance on the MART list and serious postapproval risks is the time lag between drug approval and change in labeling. We did not develop specific data tracking the first appearance of an adverse reaction that resulted in a label change. However, we can gain some insights into this issue by comparing the year of approval with whether a drug had a serious postapproval risk. Table 3.6 shows the cross-tabulation between year of approval and whether there was a serious postapproval risk. There is some variation in the proportion of drugs with serious postapproval risks year by year, but for the most part, it was approximately 50 percent from 1976 to 1982. From 1983 to 1985, the proportion of drugs with postapproval risks was slightly more than 41 percent.

Table 3.6: Year of Approval Compared With Serious Postapproval Risks

	Serious postapproval risk		
Year	No	Yes	Total
1976	10	13	**23**
1977	10	8	**18**
1978	4	13	**17**
1979	5	8	**13**
1980	5	6	**11**
1981	11	15	**26**
1982	14	13	**27**
1983	7	4	**11**
1984	13	9	**22**
1985	17	13	**30**
Total	**96**	**102**	**198**

There are two possible explanations for this decline. The first is that the FDA review process has improved and is more likely to identify the risks for a drug before approval. The second is that there has been no actual decline but, rather, serious postapproval risks for drugs approved during the later time period have not yet had sufficient time to result in label changes. The latter hypothesis seems more likely because of the strong association between appearance on the MART list and serious postapproval risks. As shown in table 3.5, 16 drugs approved between 1981 and 1985 and on the MART list do not have serious postapproval risks. Combining this with our earlier suggestion that serious additional risks may occur after 5 years, we may expect that several of the drugs not currently identified as having serious postapproval risks will in the future.

This conclusion seems to indicate that our decision to cut off our list of drugs at those approved no later than 1985 did not allow for sufficient time lag. As a result, our estimate of the number of drugs with serious postapproval risks may be low.

Association With Time Variables

The results from the logistic regression and the log-linear modeling (tables 3.2 and 3.4) suggest that drugs approved between 1976 and 1980 are almost three times as likely to have serious postapproval risks. However, as discussed above, there is the possibility that several recently approved drugs (particularly between 1983 and 1985) may have serious postapproval risks in the future. If this were to happen, the significance of the association of the period of approval with serious postapproval risk may be lower than shown above.

The results of the logistic regression analysis in table 3.2 indicated that approval in December was not strongly associated with serious postapproval risk. Thus, the results suggest that the hypothesis of a disproportionate percentage of the drugs approved in December having serious postapproval risks does not hold. In table 3.7, we compare the experience of drugs approved during December with those approved during other months. Although, as shown in the table, the number of drugs approved in December is disproportionately high, the number with serious postapproval risks is disproportionately low, contrary to what might be expected if FDA were lax in the review of these drugs.

Table 3.7: Monthly Approvals Compared With Serious Postapproval Risks

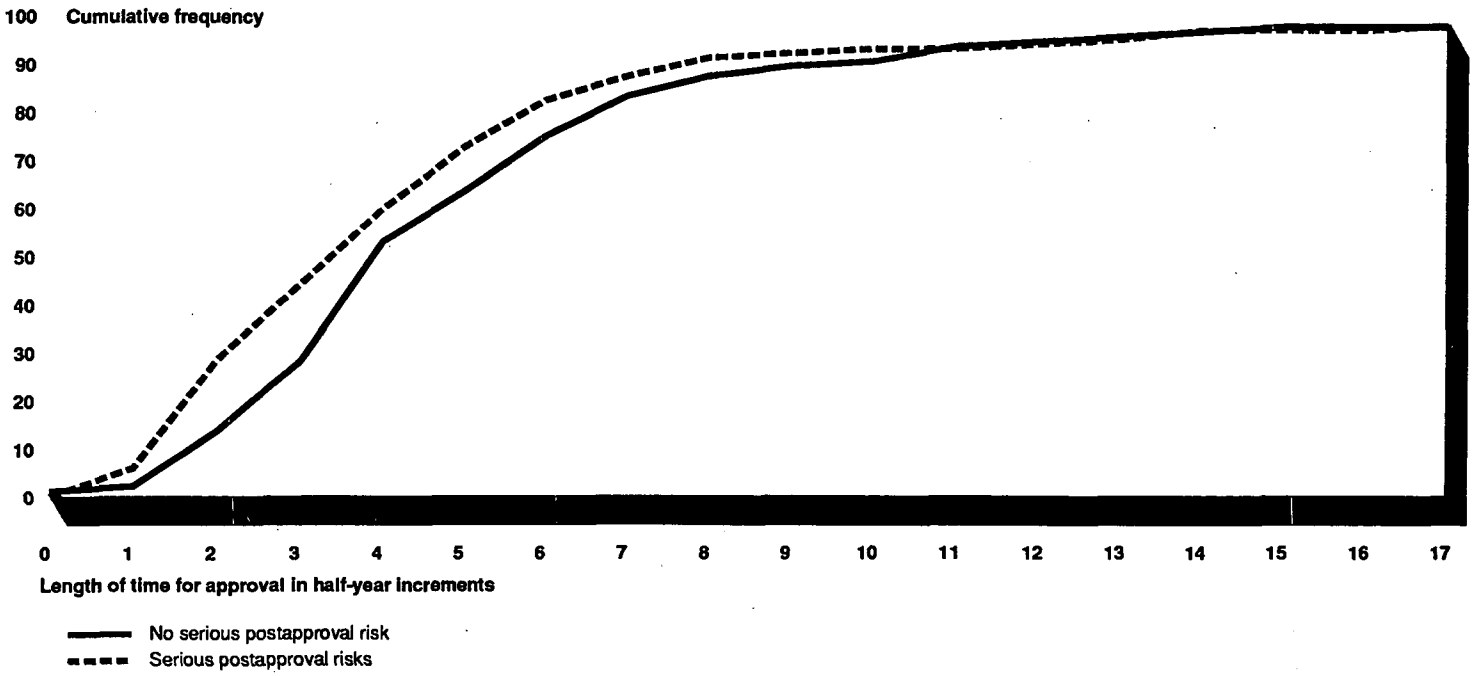
	Serious postapproval risk		
Time when approved	**No**	**Yes**	**Total**
Rest of the year	71	81	**152**
December	25	21	**46**
Total	**96**	**102**	**198**

In figure 3.1, we examine the relationship between the length of time for approval and whether a drug had a serious postapproval risk.[7] In this figure, we have rounded the length of time to the nearest 6-month increment. The relation between the two sets of drugs, those without and those with postapproval risks can be observed primarily by comparing the cumulative frequency for each category. As shown, the frequency for drugs with serious postapproval risks increases at a faster rate than that for drugs without such risks. This means that drugs with serious

[7]In the analysis, time was represented as a real number corresponding to the number of years.

postapproval risks were approved in a shorter time than drugs without. This relationship holds up to a 4-year review period, by which time more than 87 percent of the drugs in our sample had been approved.[8]

Figure 3.1: Length of Time for Approval Compared With Serious Postapproval Risks



The Relationship of Drug Class to Risk

The presentation of serious postapproval risks in table 2.1 in chapter 2 showed the breakdown by therapeutic class between drugs with and without serious postapproval risks. We did not analyze the association of therapeutic class with serious postapproval risk. However, half or more of the drugs in 12 of the 22 classes have serious postapproval risks, while one third or fewer had serious postapproval risks in 7 more of the 22 classes.

This pattern is unlikely to have arisen by chance, but it is difficult to identify characteristics of the drug classes that have a high proportion

[8]These curves were tested for differences using survival analysis techniques (the Logrank and Wilcoxon tests of significance), the survival event being the approval of the drug. Over the full range of approval times, the two curves did not differ significantly. However, when we examined only the curves for the first 4 years, the differences were significant at the 0.05 level.

of serious postapproval risks. One possible explanation is that the high-risk classes consist of drugs with an inherently greater toxicity. At first glance, that does appear to be the case for cardiac, antibiotic, anti-inflammatory, and surgical drugs (as high risk), contrasted with respiratory, neurology, metabolic-endocrine, radiopharmaceutical, and gastrointestinal drugs (as low-risk classes). However, definitive confirmation that drugs with greater toxicity are more likely to have serious postapproval risks would require the development of an index for rating the toxicity of individual drugs.

Agency Comments and Our Response

HHS questioned the adequacy of the statistical analyses presented in this chapter. (For HHS's letter, see appendix V.) Specifically, HHS questioned whether

- the result for the difference in review time between drugs with serious postapproval risks and those without serious postapproval risks was statistically significant,
- the R-squared statistic should be presented,
- the statistical significance of all the independent variables was properly presented,
- residuals were examined,
- correlations were determined for the independent variables, and
- the variable encoding appearance on the MART list should be included.

On the first point, we found that the length of time for approval is associated with serious postapproval risks when drugs that took longer than 4 years for approval (approximately 13 percent of the drugs) are not included in the analysis. Specifically, the approval time for drugs with serious risk was shorter than for drugs without serious risk. However, when all drugs are included, there is no such association. We believe this analysis is appropriate to discern whether the gap between the two curves in figure 3.1 is significant.

With respect to the remaining points HHS raised, we revised the presentation of the results of our statistical analysis to clarify our use of log-linear modeling (see pages 46-49). For the most part, HHS' discussion is not relevant to a critique of this technique, for the following specific reasons.

R-squared statistics are not, strictly speaking, appropriate for judging the adequacy of log-linear models. Likelihood ratio chi-square values indicate how well models fit the data. An R-square analog can, however,

be obtained by subtracting the chi square for the preferred model (1.23) from that of the model of independence (58.73) and then dividing that quantity by the chi square for the model of independence. In this case, we obtain (58.73 − 1.23)/58.73 = 0.979, which means that the preferred model accounts for 97.9 percent of the variation in serious postapproval risks.

In the revised presentation (particularly table 3.2), the statistical significance for all variables has been indicated.

There is no reason to analyze residuals in the log-linear models we examined. The small value of the likelihood ratio chi square (1.23 with four degrees of freedom) associated with the preferred model indicates that the differences between observed and expected frequencies can be readily attributed to sampling fluctuations or chance.

Multicollinearity is not a problem in analyzing categorical data in a multivariate format when logit-specified models (which fit or fix the associations between the independent variable) are used. All effects that the preferred model posits are net effects, or effects that remain after controlling for the associations of all factors with one another and all the effects of other factors.

It is precisely because MART is related to other variables that we examine its effect simultaneously with these others; not to do so would distort the estimates of the effects that MART and the period of approval have. In fact, each of the variables found to affect risks are significant before and after controls, or with or without MART considered in the model.

Summary and Recommendation

Our analyses of almost all new drugs approved by FDA between 1976 and 1985 provide a broader perspective on the magnitude of postapproval drug risks than it is possible to obtain from considering the development and approval of an individual drug or from considering the efficiency of the drug review process. The information and analyses we contribute here have not been previously available. The findings suggest that it would be worthwhile for FDA to build upon our results.

Summary

In chapter 2, we showed that 51.5 percent (102) of the 198 drugs we analyzed had serious postapproval risks as evidenced by labeling changes or withdrawal from the market. Several pharmacologic classes had a much higher percentage of drugs with serious postapproval risks, while other classes had a much smaller percentage. This finding indicates that the class of a drug is associated with the likelihood of serious postapproval risks.

We found that there was considerable concentration of the serious postapproval risks for certain disease categories and drug classes (frequently between three and five categories for an individual drug). We also showed that serious postapproval risks are frequently more serious manifestations of adverse effects known at the time of approval. These findings can be useful in predicting postapproval risks during the drug review process and in postmarketing surveillance.

We showed in chapter 3 that examination of several drug characteristics provided insights that can inform the drug review process and policy issues pertaining to drug approval and postmarketing surveillance. In particular, we found that drugs reviewed for use with children were over twice as likely to have serious postapproval risks and that drugs appearing on FDA's MART list were over 10 times as likely to have serious postapproval risks. We showed that drugs with serious postapproval risks had a shorter approval time than drugs without such risks. We found that there is a greater time lag (perhaps over 5 years) than expected (less than 3 years) between a drug's approval, the reporting of adverse reactions, and the subsequent changing of labels. Although these findings are not conclusive, we believe they raise questions that deserve further attention.

Recommendation

We recommend that the Commissioner of FDA establish formal systemic procedures to assure that serious risks identified after a new drug has been approved are evaluated and used to enhance premarketing review

of clinical trials and postmarketing surveillance of adverse reactions. We believe that the implementation of such procedures would, over the long run, contribute to better and more timely labeling, in both the review process and postmarketing surveillance.

We believe that FDA should, in implementing this recommendation, build upon the results developed in chapter 2, including

- identification of drugs with postapproval risks, characterized as serious and nonserious;
- enumeration of the serious postapproval risks by drug class, identifying any "class labeling" changes;
- enumeration of the serious postapproval risks by drug-induced disease category, indicating whether the category is newly identified for the drug or is an extension of less severe adverse reactions already identified for the drug and tabulating the number and type of disease categories by drug and drug class; and
- comparison of the serious and nonserious postapproval risks with the serious and nonserious risks identified at the time of approval.

For developing a system for capturing and analyzing postapproval risk information, we also suggest that FDA make an effort to introduce more quantitative risk analysis methods. To support such methods, the following kinds of information would be needed about a given drug:

- the number of people exposed to the drug,
- the proportion likely to be affected by the risk either for the general population or for specific subpopulations,
- indicators reflecting the relative significance of fatalities and morbidity (including hospitalization, prolonged hospitalization, and permanent or temporary disability), and
- the time period over which the population is exposed to the risk.

We believe this additional information would improve the understanding of postapproval risks, presenting a more definitive basis for identifying trends and informing the need for safety information prior to approval.

Agency Comments and Our Response

HHS did not concur with our recommendation as stated in the draft report. We have clarified it and more fully explained the rationale for our position. We have also rearranged the text to make specific implementation steps clearer.

New Drugs Applications Approved 1976-85

Application number	Drug generic name	Date of approval
17787	125 I fibrinogen (human)	6/28/76
18917	Acebutolol hydrochloride	12/28/84
18749	Acetohydroxamic acid	5/31/83
18604	Acyclovir	3/29/82
17835	Albumin, chromated, Cr-51, serum	2/23/76
17836	Albumin, iodinated, I-125, serum	2/23/76
17841	Albumin, iodinated, I-131, serum	2/23/76
17559	Albuterol	5/1/81
18702	Alclometasone dipropionate	12/14/82
18276	Alprazolam	10/16/81
18484	Alprostadil (PGE1)	10/16/81
18116	Amcinonide	10/18/79
50565	Amdinocillin	12/21/84
50495	Amikacin sulfate	7/12/76
18200	Amiloride hydrochloride	10/5/81
18972	Amiodarone hydrochloride	12/24/85
18021	Amoxapine	9/22/80
50564	Amoxicillin potassium clavulanate	8/6/84
18700	Amrinone lactate	7/31/84
18240	Atenolol	8/19/81
18831	Atracurium besylate	11/23/83
18689	Auranofin	5/24/85
17601	Azatadine maleate	3/29/77
50562	Azlocillin sodium	9/3/82
50520	Bacampicillin hydrochloride	12/22/80
17851	Baclofen	11/22/77
17573	Beclomethasone dipropionate	5/12/76
18250	Benoxaprofen	4/19/82
18366	Bentiromide	12/29/83
19270	Betaxolol hydrochloride	8/30/85
17675	Bethanidine sulfate	5/29/81
18770	Bitolterol mesylate	12/28/84
17954	Bretylium tosylate	7/18/78
17962	Bromocriptine	6/28/78
18225	Bumetanide	2/28/83
18401	Buprenorphine hydrochloride	12/29/81
18644	Bupropion hydrochloride	12/30/85
19215	Butoconazole nitrate	11/25/85
17857	Butorphanol tartrate	8/22/78
18312	Calcifediol	8/5/80

(continued)

Application number	Drug generic name	Date of approval
18044	Calcitriol	8/17/78
18343	Captopril	4/6/81
17989	Carboprost tromethamine	1/9/79
17422	Carmustine (BCNU)	3/7/77
50521	Cefaclor monohydrate	4/4/79
50512	Cefadroxil monohydrate	2/17/78
50504	Cefamandole nafate	9/27/78
50579	Cefonicid sodium	5/22/84
50551	Cefoperazone sodium	11/18/82
50554	Ceforanide	5/24/84
50547	Cefotaxime sodium	3/11/81
50588	Cefotetan disodium	12/27/85
50517	Cefoxitin sodium	10/18/78
50578	Ceftazidime	7/19/85
50560	Ceftizoxime sodium	9/15/83
50585	Ceftriaxone sodium	12/21/84
50558	Cefuroxime sodium	10/19/83
18757	Cellulose sodium phosphate	12/28/82
18296	Ceruletide	12/24/81
18513	Chenodiol	7/28/83
17594	Chloroxine	10/19/76
18663	Chymopapain	11/10/82
18748	Ciclopirox olamine	12/30/82
17920	Cimetidine	8/16/77
18067	Cinoxacin	6/13/80
18057	Cisplatin	12/19/78
17661	Clemastine fumarate	2/25/77
19322	Clobetasol propionate	12/27/85
17765	Clocortolone pivalate	8/22/77
17563	Colestipol	4/4/77
50508	Cyclacillin	9/14/79
17821	Cyclobenzaprine hydrochloride	8/26/77
50573	Cyclosporine	11/14/83
17557	Danazol	6/21/76
50484	Daunorubicin hydrochloride	12/19/79
17922	Desmopressin acetate	2/21/78
17856	Desoximetasone	2/28/77
17744	Difenoxin and atropine	7/14/78
17741	Diflorasone diacetate	9/14/77
18445	Diflunisal	4/19/82
18602	Diltiazem	11/5/82

(continued)

Application number	Drug generic name	Date of approval
17944	Dimercaptosuccinic acid	5/18/82
17788	Dimethyl sulfoxide	4/4/78
17810	Dinoprostone	8/23/77
17447	Disopyramide	8/31/77
17820	Dobutamine hydrochloride	7/18/78
18651	Dronabinol	5/31/85
18751	Econazole nitrate	12/23/82
18998	Enalapril maleate	12/24/85
18045	Estramustine phosphate sodium	12/24/81
17751	Etidocaine hydrochloride	8/30/76
17831	Etidronate disodium	9/1/77
18227	Etomidate	9/7/82
18768	Etoposide	11/10/83
17604	Fenoprofen calcium	3/16/76
18830	Flecainide acetate	10/31/85
18148	Flunisolide	9/24/81
17478	Gallium citrate Ga-67	5/17/76
18422	Gemfibrozil	12/21/81
17783	Glipizide	5/8/84
17498	Glyburide	5/1/84
18123	Gonadorelin hydrochloride	9/30/82
18587	Guanabenz acetate	9/7/82
18104	Guanadrel sulfate	12/29/82
17736	Halazepam	9/24/81
18780	Human insulin, regular	10/28/82
50587	Imipenem-cilastatin sodium	11/26/85
18538	Indapamide	7/6/83
19044	Indium In-111 oxyquinoline	12/24/85
18203	Intravenous fat emulsion	5/16/79
18289	Iodohippurate sodium I-123	12/28/84
18956	Iohexol	12/26/85
18735	Iopamidol	12/31/85
18905	Ioxaglate meglumine	7/26/85
17624	Isoflurane	12/18/79
18310	Isosulfan blue	7/29/81
18662	Isotretinoin	5/7/82
18533	Ketoconazole	6/12/81
18948	L-carnitine	12/27/85
18686	Labetalol hydrochloride	8/1/84
17657	Lactulose	3/25/76
19010	Leuprolide acetate	4/9/85

(continued)

Application number	Drug generic name	Date of approval
19219	Levobunolol hydrochloride	12/19/85
17588	Lomustine	8/4/76
17694	Loperamide hydrochloride	12/28/76
17794	Lorazepam	9/30/77
18613	Malathion	8/2/82
17543	Maprotiline hydrochloride	12/1/80
50518	Meclocycline sulfosalicylate	5/30/80
18006	Meclofenamate sodium	6/25/80
17862	Metoclopramide	2/7/79
17963	Metoprolol tartrate	8/7/78
17982	Metrizamide	8/23/78
17871	Metyrosine	10/3/79
18873	Mexiletine hydrochloride	12/30/85
50549	Mezlocillin sodium	9/21/81
18654	Midazolam hydrochloride	12/20/85
18154	Minoxidil	10/18/79
19368	Monooctanoin	10/29/85
50550	Moxalactam disodium	10/6/81
18677	Nabilone	12/26/85
18063	Nadolol	12/10/79
18024	Nalbuphine hydrochloride	5/15/79
18932	Naltrexone hydrochloride	11/20/84
17581	Naproxen	3/11/76
50544	Netilmicin sulfate	2/28/83
18669	Niclosamide	5/14/82
18612	Nicotine polacrilex	1/13/84
18482	Nifedipine	12/31/81
18224	Nomifensine maleate	12/31/84
18069	Oxamniquine	7/23/80
18166	Oxprenolol hydrochloride	12/28/83
19264	Pentamidine isethionate	10/16/84
17707	Pentetate indium disodium In-111	2/18/82
18631	Pentoxifylline	8/30/84
17473	Pimozide	7/31/84
18285	Pindolol	9/3/82
50545	Piperacillin sodium	12/29/81
18147	Piroxicam	4/6/82
17415	Prazepam	12/14/76
18714	Praziquantel	12/29/82
17442	Prazosin hydrochloride	6/23/76
17535	Probucol	2/1/77

(continued)

Application number	Drug generic name	Date of approval
17638	Protirelin	11/5/76
18708	Quazepam	12/27/85
16768	Quinestrol	10/11/77
18703	Ranitidine hydrochloride	6/9/83
18859	Ribavirin	12/31/85
18280	Ritodrine hydrochloride	8/24/80
18009	Saralasin acetate	5/29/81
18290	Secretin	5/29/81
17697	Sincalide	7/21/76
50502	Sisomicin sulfate	10/29/80
17869	Sodium fluorescein 25%	11/10/76
17630	Sodium iodide I-123	3/24/76
17726	Somatotropin	7/30/76
19107	Somatrem	10/17/85
50577	Streptozocin	5/7/82
18333	Sucralfate	10/31/81
19050	Sufentanil citrate	5/4/84
18738	Sulconazole nitrate	8/30/85
18557	Sulfadoxine and pyrimethamine	10/28/81
17911	Sulindac	9/27/78
18217	Suprofen	12/24/85
17970	Tamoxifen citrate	12/30/77
18467	Technetium, Tc-99m, disofenin	3/16/82
17832	Technetium, Tc-99m, albumin	2/23/76
18163	Temazepam	2/27/81
18949	Terfenadine	5/8/85
17806	Thallous chloride Tl 201	12/15/77
50497	Ticarcillin disodium	11/9/76
18103	Ticrynafen	5/2/79
18086	Timolol maleate	8/17/78
18682	Tioconazole	2/18/83
18257	Tocainide hydrochloride	11/9/84
17628	Tolmetin sodium	3/24/76
18207	Trazodone hydrochloride	12/24/81
17892	Triazolam	11/15/82
19194	Trientine hydrochloride	11/8/85
18299	Trifluridine	4/10/80
18719	Trilostane	12/31/84
16792	Trimipramine maleate	6/12/79
18081	Valproic acid	2/28/78
18776	Vecuronium bromide	4/30/84

(continued)

Application number	Drug generic name	Date of approval
18485	Verapamil	8/12/81
50486	Vidarabine	11/26/76
18536	Xenon Xe-127	10/1/82
17518	Ytterbium Yb-169 DTPA	3/11/76
18236	Zomepirac sodium	10/28/80

Results of Label Analyses for Serious Postapproval Risks

Cardiac (I) Drugs

Serious Postapproval Risks

Amiodarone Hydrochloride

NDA 18-972, approved 12/24/85.

Serious label changes: revision of the discussion in the precautions section of hyperthyroidism from occurring in 1 to 3 percent to occurring in 2 percent with a higher incidence among patients with prior inadequate dietary iodine intake, and adding an uppercase statement that the danger lies in the possibility of arrhythmia breakthrough or aggravation possibly caused by the hyperthyroidism, giving methods for identifying this occurrence (clinical symptoms and thyroid function tests), and indicating that aggressive medical treatment is required (including dose reduction, institution of antithyroid drugs, beta-adrenergic blockers or temporary corticosteroid therapy, and suggesting delayed response to this therapy, contraindication of radioactive iodine therapy, and risk of thyroid surgery in this case).

Amrinone Lactate

NDA 18-700, approved 7/31/84.

Serious label changes: the addition to warnings section of anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people.

Atenolol

NDA 18-240, approved 08/19/81.

Serious label changes: the addition of a boxed warning about cessation of therapy for patients with coronary artery disease, noting severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias following abrupt discontinuation with other beta blockers, although there is no such report for this drug.

Diltiazem

NDA 18-602, approved 11/5/82.

Serious label changes: addition to the contraindications section of patients with acute myocardial infarction and pulmonary congestion and in the precautions section, addition of results on drug interaction studies (not done at approval) (caution with any agents affecting cardiac contractility or conduction or that would result in the competitive inhibition of metabolism; 50 percent increase in propranolol; 58 percent

in diltiazem when used with cimetidine; 20 percent increase in digoxin and potentiation of anesthetic effects).

Disopyramide

NDA 17-447, approved 08/31/77.

Serious label changes: putting several warnings in bold print, including heart failure, hypotension, heart block (first-degree), QRS widening, and anticholinergic activity (in patients with glaucoma, myasthenia gravis, or urinary retention), and adding a causative link to congestive heart failure or severe hypotension in patients with primary cardiomyopathy or inadequately compensated, poorly compensated, or uncompensated congestive heart failure, and a concern about concomitant antiarrhythmic therapy (serious negative inotropic effects or excessive conduction prolongation, with particular concern about reserving quinidine, procainamide, or propranolol for patients with life-threatening arrhythmias unresponsive to single-agent therapy), and with the addition to the warnings of sections with bold print on Q-T prolongation with possible worsening of arrhythmia (including ventricular tachycardia and ventricular fibrillation), and on hypoglycemia (in rare instances, significant lowering of blood glucose, especially in certain types of patients); in the precautions section, bold print for nonteratogenic effects in pregnancy (stimulation of contractions) and the addition of a concern about patients with cardiomyopathy, particularly myocarditis (because of the possibility of developing significant hypotension), and with hyperkalemia (in which cases, toxic effects may be enhanced); in the adverse reactions section, addition of statement that the most serious reactions are hypotension and congestive heart failure; in the overdosage section, addition of statement that death, apnea, loss of consciousness, cardiac arrhythmias, and loss of spontaneous respiration have occurred following deliberate or accidental overdose; and in the dosage and administration section, in bold print, for patients with cardiomyopathy or possible cardiac decompensation, elimination of loading dose and reduction in frequency of dosing and, in lowercase, lengthening of dosing interval for patients with renal insufficiency.

Flecainide Acetate

NDA 18-830, approved 10/31/85.

Serious label changes: the addition to the adverse reactions section of myocardial infarction and, in the dosage and administration section, lower dose for patients with severe renal impairment and plasma monitoring for those with renal or hepatic impairment (with a concomitant

	change in the precautions section for those with severe hepatic impairment that slower elimination should preclude use, unless benefits outweigh risks, and then with frequent plasma monitoring).
Metoprolol Tartrate	NDA 17-963, approved 8/7/78. Serious label changes: additions to and boxing of the warnings section on myocardial infarction, warning about abrupt cessation of therapy, particularly in patients with ischemic heart disease, and warning about the possibility of unrecognized coronary artery disease (with concomitant additions to precautions section, warning such patients against cessation of therapy, to report any breathing difficulties, and to notify doctors before surgery).
Nadolol	NDA 18-063, approved 12/10/79. Serious label changes: reduction in the usual maintenance dose (for angina pectoris, from 80-240 mg/day to 40-80 mg/day, with doses up to 160 or 240 mg/day if needed, and for hypertension, from 80-320 mg/day to 40-80 mg/day, with doses up to 240-320 if needed) and maximum dose that should be used (for hypertension, from 640 mg/day to 320 mg/day).
Nifedipine	NDA 18-482, approved 12/31/81. Serious label changes: addition to the warnings section of rare possible acute myocardial infarction among those with severe obstructive coronary artery disease and the addition to the adverse reactions section of exfoliative dermatitis, erythema multiforme, and Stevens-Johnson syndrome.
Pindolol	NDA 18-285, approved 9/3/82. Serious label changes: reduction of the initial dose (from 10 mg twice a day to 5 mg twice a day) and increase in intervals at which dose may be adjusted (from 2-3 weeks to 3-4 weeks).
Tocainide Hydrochloride	NDA 18-257, approval 11/9/84. Serious label changes: boxing of previously included warning of blood dyscrasia, with additions noting sequelae such as septicemia and septic shock at recommended dosage levels with fatalities at 25 percent of

reported agranulocytosis cases (with concomitant changes in the indications and usage section, suggesting use of other alternatives for less serious arrhythmias, and in the precautions section, adding information for patients telling them to report any signs of infections that may indicate blood dyscrasia, and in the adverse reactions section, adding septicemia and shock) and additions to the adverse reactions section (based on marketing experience) of (less than 1 percent) vasculitis, bone marrow depression, hemolytic anemia, neutropenia, eosinophilia, and also (reports ascribed to underlying condition of the patient) renal failure, renal dysfunction, myocardial infarction, cerebrovascular accidents, and transient ischemic attacks.

Verapamil

NDA 18-485, approved 8/12/81.

Serious label changes: the addition, in bold print, in the indications and usage section, excepting patients for whom flutter or fibrillation is associated with accessory bypass tracts, as a potential life-threatening adverse response; a bold statement in the precautions section about severe hemodynamic effects in neonates and infants; the addition of four groups for whom the drug is contraindicated (patients with atrial flutter or fibrillation and an accessory bypass tract because of the risk of ventricular tachyarrhythmia including ventricular fibrillation, those with wide-complex ventricular tachycardia because of a risk of marked hemodynamic deterioration and ventricular fibrillation, those with hypersensitivity, and those with a functioning artificial ventricular pacemaker); addition in the warnings section for those receiving quinidine (because of a possible exaggerated hypotensive response); addition to the precautions section under drug interactions of severe adverse effects with beta-adrenergic blockers or disopyramide, exaggerated hypotensive response with alpha-adrenergic blockers, cardiovascular response with intravenous dantrolene sodium, excessive cardiovascular depression with inhalation anesthetics and calcium antagonists, and potentiation of neuromuscular blocking agents; the addition to the adverse reactions section of Stevens-Johnson syndrome, exfoliative dermatitis, erythema multiforme, skin necrosis, epidermal necrolysis, and anaphylaxis; and an addition in the dosage and administration section of a bold uppercase statement that "slow injection" should be "under continuous electrocardiographic and blood pressure monitoring."

No Serious Postapproval Risks

Acebutolol Hydrochloride	NDA 18-917, approved 12/28/84.
Bretylium Tosylate	NDA 17-954, approved 7/18/78.
Labetalol Hydrochloride	NDA 18-686, approved 8/1/84.
Mexiletine Hydrochloride	NDA 18-873, approved 12/30/85.
Pentoxifylline	NDA 18-631, approved 8/30/84.

Drugs Not Analyzed

Oxprenolol Hydrochloride	NDA 18-166, approved 12/28/83.

Antihypertensive and Renal Drugs

Serious Postapproval Risks

Alprostadil (PGE1)	NDA 18-484, approved 10/16/81. Serious label change: addition of convulsions to the adverse reactions section.
Captopril	NDA 18-343, approved 4/6/81. Serious label changes: the considerable expansion of warning about neutropenia and agranulocytosis, giving rates of occurrence in patients with various characteristics, and reporting fatality rate of 13 percent of the cases of neutropenia, almost all in patients with serious illness (collagen vascular disease, renal failure, heart failure, or immunosuppressant therapy, or a combination).
Dobutamine Hydrochloride	NDA 17-820, approved 7/18/78.

Serious label changes: addition to the warnings section of allergic-type reactions to sodium bisulfite (anaphylactic symptoms and life-threatening or less severe asthmatic episodes).

Enalapril Maleate

NDA 18-998, approved 12/24/85.

Serious label changes: addition to the contraindications section of patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor; addition to the warnings section (identification of additional patient groups at high risk—possibly fatal: those with hyponatremia, on high dose diuretic therapy, or with ischemic heart or cerebrovascular disease); addition to the precautions section (about possible change in renal function in susceptible patients such as those with severe heart failure, including oliguria, progressive azotemia, acute renal failure, and death, with bold warning to include assessment of renal function); and additions to the adverse reactions section (myocardial infarction or cerebrovascular accident, renal failure, oliguria, renal dysfunction, agranulocytosis, bone marrow depression, leukopenia, blood dyscrasia, myeloid maturation arrest, erythema multiforme, Stevens-Johnson syndrome, hepatitis, and cholestatic jaundice).

Minoxidil

NDA 18-154, approved 10/18/79.

Serious label changes: the addition to the warnings section of ischemia of special sense organs with decrease or loss of hearing or vision in patients with compromised circulation or cryoglobulinemia.

Ticrynafen

NDA 18-103, approved 5/2/79.

Serious label changes: in the precautions section, under the discussion of fluid intake, placing the original precaution in bold print, along with the addition in bold print that substantial uricosuria occurs within hours of the first dose, so that in patients receiving other diuretics or with congestive heart failure diuretics should be discontinued for 1, 2, or 3 days before beginning ticrynafen; addition to the adverse reactions section of reports (occasionally, in patients switched from another diuretic) of nausea, vomiting, flank pain, azotemia, oliguria, and rarely, anuria, reversible upon discontinuance, occurring without a washout period or adequate hydration; and addition to the dosage and administration section of "adequate fluid intake" for up to 3 days before instituting ticrynafen therapy, with addition that diuretic therapy should be interrupted for 3 days in hypertension and 1 to 2 days for salt and water

retention states associated with congestive cardiac failure. (Drug withdrawn for safety reasons, because of severe hepatic injury, including death.)

No Serious Postapproval Risks

Amiloride Hcl	NDA 18-200, approved 10/5/81.
Bumetanide	NDA 18-225, approved 2/28/83.
Cellulose Sodium Phosphate	NDA 18-757, approved 12/28/82.
Guanabenz Acetate	NDA 18-587, approved 9/7/82.
Guanadrel Sulfate	NDA 18-104, approved 12/29/82
Indapamide	NDA 18-538, approved 7/6/83.
Metyrosine	NDA 17-871, approved 10/3/79.
Prazosin Hcl	NDA 17-442, approved 6/23/76.
Saralasin Acetate	NDA 18-009, approved 5/29/81.

Drugs Not Analyzed

Bethanidine Sulfate	NDA 17-675, approved 5/29/81.

Neurology Drugs

Serious Postapproval Risks

Valproic Acid	NDA 18-081, approved 2/28/78.

Serious label changes: addition to the contraindications section in uppercase that contraindicated in patients with hepatic disease or significant

dysfunction; addition to the indications and usage section of uppercase reference to warnings section for discussion of hepatic dysfunction; additions to the warnings section: (1) in boxed warning at beginning of label and repeated in bold print in warnings section of hepatic failure resulting in fatalities, with the addition (in the boxed warning and in bold print) that children under 2 are at considerable increased risk (especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders, and those with organic brain disease) and that hepatotoxicity may be preceded by various nonspecific disorders (loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia, and vomiting), with the possibility that serum biochemistry may not always be abnormal and (in bold print only) that hepatic dysfunction may progress in spite of drug discontinuation (but that the presence of suspected or apparent significant hepatic dysfunction should lead to drug discontinuation) and (2) addition in uppercase under usage in pregnancy (a) that the drug may produce an increased incidence of birth defects (with administration to women of child-bearing potential only if shown to be essential for management of seizures) and teratogenic effects (with addition in lowercase providing additional detail from animal studies about skeletal abnormalities, fetal resorptions, and soft-tissue abnormalities, with change about postnatal growth and survival from unaffected to adversely affected—particularly when administration spanned the entire gestation and early lactation period) and (b) that the incidence of neural tube defects in the fetus may be increased during the first trimester (1-2 percent children with spina bifida) (with these additions under usage in pregnancy changed from reports suggesting an association, but one that was based on less systematic or anecdotal reports and not to be regarded as adequate to prove a definite cause and effect relationship, but rather containing intrinsic methodological problems); in the precautions section, addition under hepatic dysfunction of reference in uppercase to boxed warning, contraindications, and warnings sections and under drug interactions, revision of uppercase cautions about use with phenobarbital and phenytoin from unknown effects to severe CNS depression in the case of phenobarbital (including without elevations of serum levels) and breakthrough seizures in the case of phenytoin (with various changes in the serum concentration), with addition that primidone is metabolized into a barbiturate that may be involved in a similar or identical interaction; and additions to the adverse reactions section of rare cases of coma (when receiving valproic acid alone as well as with phenobarbital), thrombocytopenia, petechiae, bruising, hematoma formation, frank hemorrhage, hypofibrinogenemia, eosinophilia, anemia, bone marrow

suppression, and increases in serum bilirubin and abnormal changes in other liver function tests (possibly reflecting serious hepatotoxicity).

No Serious Postapproval Risks

Baclofen	NDA 17-851, approved 11/22/77.
Cyclobenzaprine Hcl	NDA 17-821, approved 8/26/77.
Dronabinol	NDA 18-651, approved 5/31/85.
Nabilone	NDA 18-677, approved 12/26/85.

Drugs Not Analyzed

None.

Psychopharmacologic Drugs

Serious Postapproval Risks

Alprazolam — NDA 18-276, approved 10/16/81.

Serious label changes: additions in the precautions, adverse reactions, drug abuse and dependence, and dosage and administration sections concerning withdrawal seizures upon rapid decrease or abrupt discontinuation (indicating actual reports in patients receiving recommended or higher doses and suggesting gradual reduction of no more than 0.5 mg every three days) and addition to the adverse reactions section of rage as a paradoxical reaction "as with all benzodiazepines."

Amoxapine — NDA 18-021, approved 9/22/80.

Serious label changes: addition to the warnings and adverse reactions sections of potentially fatal neuroleptic malignant syndrome; addition to the warnings, precautions, and adverse reactions sections of reports of

tardive dyskinesia (with advice about this possibility to be communicated to the patient); and addition to the overdosage section that this drug differs significantly from other tricyclic antidepressants with frequent CNS effects, particularly grand mal convulsions, and also status epilepticus, coma, acidosis, renal failure, and acute tubular necrosis with rhabdomyolysis and myoglobinuria.

Bupropion Hydrochloride

NDA 18-644, approved 12/30/85.

Serious label changes: in the warnings section, (1) change in bold print warning from "greater epileptogenic potential . . . with a non-excessive risk of seizures at doses up to 450 mg/day" to listing of incidence of seizures (4/1,000) at doses up to 450 mg/day, said to be as much as fourfold that of other antidepressants, (2) addition in bold print of recommendations for reducing seizure risk (largely moved from dosage and administration section and put into bold print), with addition that a single dose should not exceed 150 mg, and (3) addition in bold print of further circumstances calling for extreme caution (history of predispositions toward seizure, naming of other predisposing agents—antipsychotics and other antidepressants, and addition of treatment regimens as contributory—specifically, abrupt discontinuation of a benzodiazepine); addition to the contraindications section of patients with bulimia or anorexia nervosa because of a higher incidence of seizures; in the indications and usage section, change from indication for those who fail to respond or tolerate alternatives and not as antidepressant of first choice (because of high risk of seizures at 600 mg/day) to addition of advice for physicians to consider high risk of generalized seizures (4/1,000); and in the dosage and administration section, (1) addition of usual dose (300 mg/day), change from previous implied dose of 450 mg/day, (2) reduction in starting dose (from 225 to 200 mg/day), (3) reduction in amount of increase (from addition of 75 mg/day up to maximum of 450 mg/day to addition of 100 mg up to 300 mg/day, not to be made until the fourth day of treatment), and (4) addition of a section on increasing the dosage above 300 mg/day (not to occur until no improvement noted after several weeks, with limit of 150 mg per dose, at least 4 hours between doses, and discontinuance if no clinical effect shown at 450 mg/day).

Maprotiline Hydrochloride

NDA 17-543, approved 12/01/80.

Serious label changes: addition to the warnings section in bold print that seizures are associated with use (particularly with rapid dosage escalation or tapering), along with addition of pertinent information (confounding factors including other seizure threshold lowering drugs, dosage beyond therapeutic range, concomitant use with phenothiazines, and suggestions for reducing seizure risk); addition to the precautions section of information to be given to the patient about the risk of seizures; and change in the overdosage section from the recommended use of physostigmine to exclusion because of its increased risk of seizures.

Midazolam Hydrochloride

NDA 18-654, approved 12/20/85.

Serious label changes: in the warnings section, addition of boxed warning about respiratory depression and respiratory arrest, with possible death or hypoxic encephalography, and about dosing, particularly warning against bolus injections; in the warnings section, change to bold print from raised capitals of warning about availability of oxygen and resuscitative equipment; in the warnings section, addition of bold print warning about individualization of dosage and continuous monitoring and against rapid or single bolus intravenous administration; in the adverse reactions section, addition of bold print reference to warnings section for serious cardiorespiratory events and possible paradoxical reactions; in the dosage and administration section, replacement of general statement about individualization of dosage, lower doses for the elderly, adjustment based on premedication, availability of equipment to maintain patent airway with bold print statement that slow administration and individualization of dosage are required and addition, under intravenous administration, of recommendation that 1 mg/ml formulation be used to facilitate slower injection, warning about individualizing dosage and taking into account various factors; addition, in the dosage and administration section, of directions for administering to desired effect (including details about amounts, time of administration, waiting to evaluate sedative effect, reduction for premedication, and adjustments for elderly or debilitated patients); and additions to the adverse reactions section (convulsions, paralysis, cerebrovascular accidents, hemiplegia, and cerebral ischemia).

Nomifensine Maleate

NDA 18-224, approved 12/31/84.

Serious label changes: addition to the contraindications section of patients with severe renal impairment or with a history of severe blood dyscrasia; changes to the warnings section: (1) addition that there have

	been reports of immune mediated injury, with significant morbidity and fatal cases, including hemolytic anemia, a syndrome of fever and alveolitis, eosinophilia, necrotizing vasculitis, and a lupus-like syndrome, (2) modification of discussion of hemolytic anemia from reported after treatment from 2 weeks up to 14 months to reported with fatalities, with overall incidence unknown after both brief and prolonged treatment and after intermittent and continuous administration, with potentially life-threatening sequelae leading to acute renal failure, giving need to use blood count for baseline and to exclude hemolytic anemia and giving treatment suggestions; and addition to the adverse reactions section of kidney failure secondary to hemolytic anemia. (Drug withdrawn for safety reasons.)
Pimozide	NDA 17-473, approved 7/31/84. Serious label changes: additions to the warnings and adverse reactions sections of neuroleptic malignant syndrome (potentially fatal, including hyperpyrexia, muscle rigidity, altered mental status including catatonic signs, evidence of autonomic instability, elevated creatinine phosphokinase, myoglobinuria, and acute renal failure); addition in warnings section of information on tardive dyskinesia (prevalence, unpredictability in individual patients, possible occurrence even at low doses, absence of known treatment, possible masking of underlying process, and considerations to be used in prescribing the drug); and change in the dosage and administration section reducing the recommended maximum dose from 0.3 mg/kg/day or 20 mg/day to 0.2 mg/kg/day or 10 mg/day.
Trazodone Hydrochloride	NDA 18-207, approved 12/24/81. Serious label changes: addition to the warnings section in uppercase of an association with the occurrence of priapism, requiring surgical intervention in one-third of the cases with permanent impairment of erectile function or impotence in a portion of these cases (and with the addition of this effect to the adverse reactions section and to the precautions section under information for the patient to indicate that they should discontinue the drug and consult a physician if they experience prolonged or inappropriate penile erection).
Triazolam	NDA 17-892, approved 11/15/82. Serious label changes: additions to the precautions section that some side effects—drowsiness, dizziness, lightheadedness—appear to be dose

related and that other more serious behavioral effects—confusion, bizarre or abnormal behavior, agitation and hallucinations—may also be; changes in the adverse reactions section: increased frequency of convulsions and (from associated generally with benzodiazepines to associated specifically with triazolam) amnestic symptoms, confusional states, restlessness, excitation, aggressiveness, falling, somnambulism, and inappropriate behavior; and changes in the dosage and administration section (recommended dosage changed from "0.25 to 0.5" to "0.25," with suggestion that 0.125 may be sufficient and that 0.5 be reserved for patients who do not respond to a lower dose because of adverse reaction).

No Serious Postapproval Risks

Halazepam	NDA 17-736, approved 9/24/81.
Lorazepam	NDA 17-794, approved 9/30/77.
Prazepam	NDA 17-415, approved 12/14/76.
Quazepam	NDA 18-708, approved 12/27/85.
Temazepam	NDA 18-163, approved 2/27/81.
Trimipramine Maleate	NDA 16-792, approved 6/12/79.

Drugs Not Analyzed

None.

Drug Abuse Drugs

Serious Postapproval Risks

Buprenorphine Hydrochloride — NDA 18-401, approved 12/29/81.

Serious label changes: addition to the warnings section that clinically significant respiratory depression may occur with the recommended

dose range and that particular caution is advised in patients receiving CNS-respiratory depressant drugs, recommending that patients with risk factors have their dosage reduced by half and adding in uppercase bold print that naloxone may not be effective in reversing the respiratory depression (as previously suggested) (with concomitant changes to the precautions, overdosage, and dosage and administration sections reflecting these concerns and with additional explanation in the clinical pharmacology section that slow dissociation from its receptor may account for unpredictability of its reversal by opioid antagonists, and with removal of reports of clinical studies of effects on respiration that depression occurred above therapeutic doses although severe respiratory depression was possible at therapeutic doses in predisposed individuals); addition to the adverse reactions section of increased frequency of apnea; in the overdosage section, revision of manifestations to indicate that signs cannot be defined but that respiratory depression may occur at therapeutic doses, whereas previously stated that doses 10 to 20 times the normal dose had been administered safely and that overdosage effects of CNS depression were to be extrapolated from animal pharmacology; in the overdosage section, revision of manifestations to indicate that signs cannot be defined but that respiratory depression may occur at therapeutic doses, whereas previously stated that doses 10 to 20 times the normal dose had been administered safely and that overdosage effects of CNS depression were to be extrapolated from animal pharmacology; and addition to the drug abuse and dependence section that it may induce withdrawal symptoms in acutely dependent narcotic addicts.

Butorphanol Tartrate

NDA 17-857, approved 08/22/78.

Serious label changes: addition to the adverse reactions section of (less than 1 percent) seizures and apnea and addition to the dosage and administration section of reduction in dosage when used with phenothiazines and other tranquilizers that may potentiate the drug's action.

Nalbuphine Hcl

NDA 18-024, approved 05/15/79.

Serious label changes: additions to the warnings section: (1) in bold print that administration should be by persons specifically trained and that resuscitative equipment and oxygen should be readily available and (2) warning about sulfites sensitivity with allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, with overall prevalence unknown and addition of instructions

for use as a supplement to balanced anesthesia, with precaution for respiratory depression reversible with naloxone hydrochloride.

No Serious Postapproval Risks

Naltrexone Hydrochloride — NDA 18-932, approved 11/20/84;

Nicotine Polacrilex — NDA 18-612, approved 1/13/84.

Drugs Not Analyzed

None.

Fertility-Antifertility Drugs

Serious Postapproval Risks

Danazol — NDA 17-557, approved 6/21/76.

Serious label changes: in the warnings section, addition in bold print that (1) since safe use in pregnancy has not been established, a nonhormonal method of contraception should be used because of possible androgenic effect, (2) this has been limited to clitoral hypertrophy and labial fusion, and (3) the patient should be apprised of the potential risk to the fetus; additions in the adverse reactions section of testicular atrophy and clitoral hypertrophy under androgenic effects, and of liver necrolysis and hepatotoxicity; and, in the dosage and administration section, additions in bold print (1) that therapy should begin during menstruation or after appropriate tests to ensure that the patient is not pregnant and (2) that therapy should continue for 3 to 6 months.

Dinoprostone — NDA 17-810, approved 8/23/77.

Serious label changes: the addition to the contraindications section of patients with active cardiac, pulmonary, renal, or hepatic disease and the removal from the boxed warning about use in a hospital setting only

for the indication of termination of pregnancy in the 12th through 20th gestational week (thus extending the warning to all indications).

Ritodrine Hydrochloride

NDA 18-280, approved 8/24/80.

Serious label changes: in the warnings section, (1) change in boxed warning, from maternal pulmonary edema reported rarely when used concomitantly with corticosteroids, to reported with use of ritodrine, with or without corticosteroids although more frequently with and sometimes after delivery with maternal death, requiring careful monitoring of state of hydration, avoiding fluid overload, with particular concern about aggravation from betamimetics, (2) addition of warning about use of beta-adrenergic drugs as possibly leading to myocardial ischemia, with complications including myocardial necrosis (possibly resulting in death), arrhythmias (including premature atrial and ventricular contractions, ventricular tachycardia, and bundle branch block), and anginal pain (with or without ECG changes), (3) addition to italicized warning about cardiovascular responses to be alert for persistent high tachycardia, chest pain, or tightness of chest, and (4) addition of warning about possible sulfite-caused allergic type reaction including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people; addition to the precautions section under drug interactions that cardiovascular effects (especially cardiac arrhythmia or hypotension) may be potentiated by magnesium sulfate, diazoxide, meperidine, potent general anesthetic agents and systemic hypertension by the presence of parasympatholytic agents such as atropine; additions to the adverse reactions section: (1) that persistent high tachycardia may be a sign of impending pulmonary edema (with reference to warnings section), (2) underlined addition of (less than 1 percent) impaired liver function (increased transaminase levels and hepatitis) with the use of ritodrine and other beta sympathomimetics, and (3) under cardiac symptoms, reference to warnings section; and additions to the dosage and administration section: (1) under method of administration that fluid overload must be avoided, (2) change of diluents, removing several, and stating that saline solutions should be reserved for cases where dextrose solution is medically undesirable (e.g., diabetes mellitus) because of increased probability of pulmonary edema, (3) a more concentrated solution may be prepared where fluid restriction is medically desirable, (4) reference to precautions for monitoring against fluid overload, and (5) of frequent monitoring of maternal uterine contractions, heart rate, blood pressure, and fetal heart rate.

No Serious Postapproval Risks

Carboprost Tromethamine	NDA 17-989, approved 1/9/79.
Quinestrol	NDA 16-768, approved 10/11/77.

Drugs Not Analyzed

None.

Metabolic and Endocrine (I) Drugs

Serious Postapproval Risks

Glipizide	NDA 17-783, approved 5/8/84. Serious label changes: addition to the adverse reactions section of exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, erythema nodosum, skin necrolysis, and epidermal necrolysis.
Glyburide	NDA 17-498, approved 5/01/84. Serious label changes: addition to the adverse reactions section of exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, erythema nodosum, skin necrolysis, and epidermal necrolysis.

No Serious Postapproval Risks

Calcifediol	NDA 18-312, approved 8/5/80.
Calcitriol	NDA 18-044, approved 8/17/78.
Desmopressin Acetate	NDA 17-922, approved 2/21/78.
Etidronate Disodium	NDA 17-831, approved 9/1/77.

L-Carnitine	NDA 18-948, approved 12/27/85.
Somatrem	NDA 19-107, approved 10/17/85.
Trilostane	NDA 18-719, approved 12/31/84.

Drugs Not Analyzed

None.

Metabolic and Endocrine (II) Drugs

Serious Postapproval Risks

Bromocriptine

NDA 17-962, approved 6/28/78.

Serious label changes: additions to the contraindications section that the drug is contraindicated in patients with uncontrolled hypertension (with addition, mostly in relation to the new indication of postpartum prevention of physiologic lactation, of a warning about decreases in supine systolic and diastolic pressures—as much as 50-59 mm of Hg, and bold print warnings about hypertension with seizures (including status epilepticus and stroke) with progressively severe headache and visual disturbances (blurred vision and transient cortical blindness), and acute myocardial infarction; and additions to the adverse reactions section of decreases in blood pressure, seizures, stroke, myocardial infarction, headache, and visual disturbances); addition to the precautions section of a subsection on drug interactions with concern about drugs with dopamine antagonist activity or any other ergot derivatives; and in the adverse reactions section addition of psychosis, hallucinations, paranoid reactions, depression, and catatonic reactions.

Gemfibrozil

NDA 18-422, approved 12/21/81.

Serious label changes: in the indications and usage section, modification of specifications for treatment of very high elevations of serum triglycerides (change from 750 mg/dl to over 2,000 mg/dl with elevations of VLDL-cholesterol as well as fasting chylomicrons, with therapy to be

considered with triglyceride levels between 1,000 and 2,000 with a history of pancreatitis or recurrent abdominal pain, and indicating inadequately studied results for patients below 1,000 mg/dl who convert to a Type V pattern); in the warnings section, addition of discussion of the Helsinki Heart Study, which showed that (1) excess mortality (particularly noncoronary heart disease) for gemfibrozil is not statistically significantly different from 29 percent excess mortality in the clofibrate group in a separate WHO study and (2) in a gallstone prevalence substudy, gemfibrozil showed a trend toward greater prevalence (55 percent excess) including gallbladder surgery, and additions that concomitant therapy with lovastatin has been associated with rhabdomyolysis, markedly elevated creatine kinase levels and myoglobinuria, leading in a high proportion of cases to acute renal failure, with risk of combined therapy outweighing benefits and that the use of fibrates alone (including Lopid) may be associated with myositis and hence any muscle pain, tenderness, or weakness should have prompt evaluation for myositis including creatine kinase levels and withdrawal of drug if myositis is suspected; in the precautions section, addition of warning about rhabdomyolysis occurring with combined gemfibrozil and lovastatin therapy; and addition, in bold print in the adverse reactions section, that musculoskeletal symptoms, abnormal liver function tests, and hematologic changes are probably causally related to gemfibrozil.

Probucol

NDA 17-535, approved 2/1/77.

Serious label changes: addition to the contraindications section of bold statement that the drug is contraindicated in patients with an abnormally long QT interval (along with addition of reference to the warnings section and addition of patients with evidence of recent or progressive myocardial infarction or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin) and additions to the warnings section in uppercase referring to serious animal toxicity and in bold print about prolongation of the QT interval with serious arrhythmias on probucol alone or with an antiarrhythmic drug and that assessments of benefits must outweigh risks (along with nonbold warning about diet, ECG with stated limits, unexplained syncope, and the use of drugs that prolong the QT interval and warning that hypokalemia, hypomagnesemia, severe bradycardia, or myocardial infarction, ischemia, or inflammation should be resolved before use).

Protirelin

NDA 17-638, approved 11/05/76.

	Serious label changes: in the warnings section, concerns about transient changes in blood pressure put into uppercase with addition of uppercase statement that more severe degrees of hypertension or hypotension have been reported and, in the adverse reactions section, addition of uppercase statement of marked changes in blood pressure.
Somatotropin	NDA 17-726, approved 7/30/76. Serious label changes: (Withdrawn from the market for safety reasons, because of potential contamination of the product with Creutzfeldt-Jakob disease, which could not be definitively recognized as present or not present in the product.)

No Serious Postapproval Risks

Colestipol	NDA 17-563, approved 4/4/77.
Gonadorelin Hydrochloride	NDA 18-123, approved 9/30/82.
Leuprolide Acetate	NDA 19-010, approved 4/9/85.

Drugs Not Analyzed

Human Insulin, Regular	NDA 18-780, approved 10/28/82.

Antibiotics

Serious Postapproval Risks

Amikacin Sulfate	NDA 50-495, approved 7/12/76. Serious label changes: the addition to the boxed warning of the phrase "safety not established beyond 14 days" in connection with potential neurotoxicity when used for longer than recommended and warning about neuromuscular blockade and respiratory paralysis (especially in patients receiving anesthetics, neuromuscular blocking agents, or citrate

anticoagulated blood transfusions); the addition to the precautions section of irreversible deafness, renal failure, and death from neuromuscular blockade when used topically in association with surgical procedures (with an addition to the contraindications section of a history of hypersensitivity to other aminoglycosides), of inaccuracy of measurement of renal function in elderly patients, and of caution in patients with muscular disorders since these drugs may aggravate muscle weakness; the addition to the warnings section of a relationship of neurotoxicity and nephrotoxicity to renal impairment and other factors (advanced age and dehydration) and the identification of other manifestations of neurotoxicity (numbness, skin tingling, muscle twitching, and convulsions) and a warning about sodium bisulfite as potentially causing allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people; and the addition to the adverse reactions section of auditory, vestibular, and renal toxicity, hearing loss, loss of balance, cochlear damage, neuromuscular blockade and acute muscular paralysis.

Amoxicillin Potassium Clavulanate	NDA 50-564, approved 8/6/84. Serious label change: addition to the adverse reactions section of pseudomembranous colitis.
Cefaclor Monohydrate	NDA 50-521, approved 4/4/79. Serious label changes: in the warnings section, addition in bold print of warning about serum-sickness like reactions associated with repeated use with an incidence of 1 in 200 often resulting in hospitalization for patients presenting with hypersensitivity reactions temporally associated with use; the addition to the precautions section of caution in individuals with history of gastrointestinal disease; and the addition to the adverse reactions section of more severe hypersensitivity reactions (including toxic epidermal necrolysis and anaphylaxis, with the latter more common in patients with a history of penicillin allergy), pseudomembranous colitis, serum sickness-like reactions (including erythema multiforme and rarely, Stevens-Johnson syndrome, usually during a second course of therapy, more frequently in children, with an overall incidence of 1 in 200, and that while these have had no serious sequelae, they have resulted in hospitalization), and anaphylaxis (half in patients allergic to penicillin).
Cefadroxil Monohydrate	NDA 50-512, approved 2/17/78.

	Serious label changes: the addition of pseudomembranous colitis in the adverse reactions section and in bold print in the warnings section.
Cefamandole Nafate	NDA 50-504, approved 9/27/78.
	Serious label changes: the addition of pseudomembranous colitis in adverse reactions and warnings sections, the addition of inhibition of enzyme acetaldehyde dehyrogenase in animals (causing accumulation of acetaldehyde when ethanol is administered) in precautions section, and possibility of seizures when overdosage occurs in patients with renal impairment.
Cefonicid Sodium	NDA 50-579, approved 5/22/84.
	Serious label changes: rare reports of acute renal failure with interstitial nephritis.
Cefoperazone Sodium	NDA 50-551, approved 11/18/82.
	Serious label changes: addition to the adverse reactions section of prothrombin decrease and hemorrhage.
Cefotaxime Sodium	NDA 50-547, approved 3/11/81.
	Serious label change: the addition of pseudomembranous colitis in the warnings section.
Cefotetan Disodium	NDA 50-588, approved 12/27/85.
	Serious label changes: addition to the adverse reactions section of anaphylaxis, prothrombin decrease, and hemorrhaging.
Cefoxitin Sodium	NDA 50-517, approved 10/18/78.
	Serious label changes: the addition, in the adverse reactions section, of "infrequent" reports of anaphylaxis, pseudomembranous colitis, granulocytopenia, bone marrow depression, and acute renal failure, and, in the warnings section, a bold warning about pseudomembranous colitis.
Ceftriaxone Sodium	NDA 50-585, approved 12/21/84.

	Serious label change: addition to the adverse reactions section of hemorrhaging.
Cefuroxime Sodium	NDA 50-558, approved 10/19/83.
	Serious label changes: the addition of rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome.
Imipenem-Cilastatin Sodium	NDA 50-587, approved 11/26/85.
	Serious label changes: in the precautions sections, addition that CNS adverse experiences occur especially when recommended dosages were exceeded and that they have occurred in patients without compromised renal function (previously limited to those without underlying CNS disorder) and addition that seizures occurred at a higher rate in those with severe or marked impairment of renal function, with recommended close adherence to dosage regimens and careful evaluation of risks.
Mezlocillin Sodium	NDA 50-549, approved 9/21/81.
	Serious label changes: the addition of acute interstitial nephritis and pseudomembranous diarrhea to the adverse reactions section.
Moxalactam Disodium	NDA 50-550, approved 10/6/81.
	Serious label changes: addition of a boxed warning about interference with hemostasis from hypoprothrombinemia, platelet dysfunction, and, very rarely, immune-mediated thrombocytopenia (with hypoprothrombinemia upgraded from unemphasized discussion in precautions section), with dose-dependency for platelet dysfunction and with other possible factors for bleeding during therapy, and with recommended monitoring of bleeding time; in the warnings section, addition of a warning about pseudomembranous colitis reported with virtually all broad-spectrum antibiotics and ranging in severity from mild to life threatening, to be considered in all cases of diarrhea; in the adverse reactions section, change from disturbance in vitamin-K clotting function (decreased prothrombin, increased bleeding time, or thrombocytopenia) to bleeding in association with hypoprothrombinemia, decreased platelet function, or from other causes and addition of pseudomembranous colitis (during or after treatment); addition to the precautions section of caution in prescribing to individuals with a history of gastrointestinal disease; and in the dosage and administration

	section, reduction of upper value of usual daily dose from 6g to 4g, addition of recommendation for monitoring bleeding time for those who receive more than 4g for more than 3 days, and addition of recommended prophylactic vitamin K.
Netilmicin Sulfate	NDA 50-544, approved 2/28/83. Serious label changes: the addition to the warnings section of a potential for hypersensitivity reactions (including anaphylactic symptoms and life-threatening asthmatic episodes), the addition to the precautions section of tetany, paresthesias, muscle weakness with need for corrective electrolyte therapy in patients with hypomagnesemia, hypocalcemia, and hypokalemia, and a Fanconi-like syndrome with aminoaciduria and metabolic acidosis, and the addition to adverse reactions section of peripheral neuropathy or encephalopathy including numbness, skin tingling, muscle twitching, convulsions, and myasthenia-gravis-like syndrome.
Piperacillin Sodium	NDA 50-545, approved 12/29/81. Serious label changes: changes in the adverse reactions section, with the addition of rare reports of pseudomembranous colitis, erythema multiforme, Stevens-Johnson syndrome, and interstitial nephritis.
Ticarcillin Disodium	NDA 50-497, approved 11/9/76. Serious label changes: reductions in the dosage for use in neonates and the increased incidence of bleeding time.

No Serious Postapproval Risks

Amdinocillin	NDA 50-565, approved 12/21/84.
Azlocillin Sodium	NDA 50-562, approved 9/3/82.
Bacampicillin Hcl	NDA 50-520, approved 12/22/80.
Ceforanide	NDA 50-554, approved 5/24/84.
Ceftazidime	NDA 50-578, approved 7/19/85.

Ceftizoxime Sodium	NDA 50-560, approved 9/15/83.
Cyclacillin	NDA 50-508, approved 9/14/79.

Drugs Not Analyzed

Sisomicin Sulfate	NDA 50-502, approved 10/29/80.

Dermatologic Drugs

Serious Postapproval Risks

Amcinonide	NDA 18-116, approved 10/18/79. Serious label changes: addition to the precautions section in italics under pediatric use of a greater susceptibility to HPA axis suppression, Cushing's syndrome, hyperglycemia, and glycosuria.
Desoximetasone	NDA 17-856, approved 2/28/77. Serious label changes: addition to the precautions section in italics under pediatric use of a greater susceptibility to HPA axis suppression, Cushing's syndrome, hyperglycemia, and glycosuria.
Diflorasone Diacetate	NDA 17-741, approved 9/14/77. Serious label changes: addition to the precautions section in italics under pediatric use of a greater susceptibility to HPA axis suppression, Cushing's syndrome, hyperglycemia, and glycosuria.
Isotretinoin	NDA 18-662, approved 5/7/82. Serious label changes: addition of a boxed contraindication that the drug is not to be used by pregnant females or those who intend to become pregnant (because of major fetal abnormalities that have been reported), with pregnancy test within 2 weeks prior to therapy, effective form of contraception for 1 month following therapy, counseling on

	the serious risk to the fetus, and discussion about continuing the pregnancy if it should occur (previously, section contained only teratogenicity in animals); addition of boxed warning concerning the occurrence of pseudotumor cerebri with early symptoms including papilledema, headache, nausea, and vomiting, with drug discontinuance and referral to neurologist if present (with addition of pseudotumor cerebri to the adverse reactions section); addition of bold statement to the precautions section under information for patients that women of child-bearing potential should not be pregnant and should use an effective form of contraception, with reference to boxed contraindication; addition to the adverse reactions section in bold print that most adverse reactions were reversible when therapy was discontinued but some persisted after cessation of therapy; and changes in the dosage and administration section: (1) lower dosage from 1.0 mg/kg to 0.5 mg/kg, with report showing initial clearing of disease at all levels (from 0.1 to 1 mg/kg/day) but with greater need for retreatment at lower doses, (2) instead of individualizing initial dose to weight and disease severity, now recommended at 0.5 to 1 mg/kg/day, but with allowance for up to 2 mg/kg/day for very severe cases or ones whose disease is primarily on the body, and dose adjustment based on side effects now noted as being dose-related.
Malathion	NDA 18-613, approved 8/2/82. Serious label changes: placing the warning about flammability and exposure to open flame or hair dryers into box, adding concern about any electric heat or smoking while applying lotion or hair is wet.
Meclocycline Sulfosalicylate	NDA 50-518, approved 5/30/80. Serious label changes: addition to the warnings section of concern about sulfite sensitivity with allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes.

No Serious Postapproval Risks

Alclometasone Dipropionate	NDA 18-702, approved 12/14/82.
Chloroxine	NDA 17-594, approved 10/19/76.
Ciclopirox Olamine	NDA 18-748, approved 12/30/82.

Clobetasol Propionate	NDA 19-322, approved 12/27/85.
Clocortolone Pivalate	NDA 17-765, approved 8/22/77.
Econazole Nitrate	NDA 18-751, approved 12/23/82.
Sulconazole Nitrate	NDA 18-738, approved 8/30/85.

Drugs Not Analyzed

Tioconazole	NDA 18-682, approved 2/18/83.

Anti-Infective Drugs

Serious Postapproval Risks

Acyclovir	NDA 18-604, approved 3/29/82.
	Serious label changes: additions to the adverse reactions section of acute kidney failure, abnormal kidney function, polyneuritis, and agranulocytosis.
Ketoconazole	NDA 18-533, approved 6/12/81.
	Serious label changes: in the warnings section, addition of a boxed warning about hepatotoxicity (including fatalities), addition of a bold print warning giving reported incidence (1:10,000), median duration of treatment (28 days), indicating usual reversibility and indicating several cases of hepatitis in children (recommending liver function tests before and during treatment, particularly for patients receiving hepatotoxic drugs or with a history of liver disease), and addition of bold print warning of rare cases of anaphylaxis; addition to the precautions section of information for patients in bold print warning about any signs or symptoms of liver dysfunction; and in the adverse reactions section, addition in bold print of anaphylaxis after the first dose and addition that, although most reactions are mild, the rare occurrences of liver dysfunction require prompt attention.

No Serious Postapproval Risks

Butoconazole Nitrate	NDA 19-215, approved 11/25/85.
Cinoxacin	NDA 18-067, approved 6/13/80.
Pentamidine Isethionate	NDA 19-264, approved 10/16/84.
Ribavirin	NDA 18-859, approved 12/31/85.

Drugs Not Analyzed

None.

Ophthalmics

Serious Postapproval Risks

Levobunolol Hydrochloride

NDA 19-219, approved 12/19/85.

Serious label changes: addition to the contraindications section of patients with sinus bradycardia, second and third degree atrioventricular block, overt cardiac failure, or cardiogenic shock; in the warnings section, addition that the same adverse reactions as with systemic administration of beta-adrenergic blocking agents may occur with topical administration, including severe respiratory reactions, cardiac reactions including rarely death from bronchospasm in patients with asthma, and addition of warnings about cardiac failure (more severe failure may be precipitated in patients with diminished myocardial contractility), cardiac failure from continued depression of the myocardium (in patients with such history), bronchodilation in patients with nonallergic bronchospasm, potential protracted severe hypotension during major surgery from impaired ability to respond to beta-adrenergically mediated reflex stimuli, and allergic-type reactions from sulfites including anaphylactic symptoms or less severe asthmatic episodes; and in the adverse reactions section, addition of heart block, cerebral vascular accident, and cerebral ischemia.

Sodium Fluorescein 25%

NDA 17-869, approved 11/10/76.

	Serious label changes: addition of whole warnings section with inclusion of most severe adverse reactions (cardiac arrest, acute myocardial infarction, basilar artery ischemia, severe shock and other signs and symptoms of hypersensitivity, convulsions, syncope, thrombophlebitis at the injection site, and transient dyspnea, with those not underlined previously mentioned in the adverse reactions section); addition to the adverse reactions section of rare cases of death; addition in bold print to the precautions and dosage and administration section that an emergency tray (including epinephrine, antihistamine, soluble steroid, aminophylline, and oxygen) should be available for possible reaction (previously a caution in the dosage and administration section, mentioning only epinephrine and antihistamine); and in the dosage and administration section, reduction of children's dosage from 0.28 ml per 10 pounds to 0.02 ml for each pound.
Timolol Maleate	NDA 18-086, approved 8/17/78. Serious label changes: addition to the contraindications section of patients with bronchial asthma or with a history of bronchial asthma or severe chronic obstructive pulmonary disease, sinus bradycardia, second and third degree atrioventricular block, overt cardiac failure (with corresponding additions in the warnings section about use in various types of patients, including those with cardiac failure, in whom more failure may be precipitated, and in patients without a history of cardiac failure, in whom, over a period of time, failure may occur), or cardiogenic shock and addition to the warnings section in bold print that the same adverse reactions found with systemic administration of beta-adrenergic blocking agents (severe respiratory reactions, cardiac reactions, death from bronchospasm in patients with asthma, and death in association with cardiac failure) may occur (with the addition to the precautions section against use of two topical ophthalmic beta-blocking agents concurrently) and addition in uppercase giving warnings for use in patients with obstructive pulmonary disease, indicating that it may block bronchodilation and hence is contraindicated.

No Serious Postapproval Risks

Betaxolol Hydrochloride	NDA 19-270, approved 8/30/85.
Trifluridine	NDA 18-299, approved 4/10/80.

Vidarabine	NDA 50-486, approved 11/26/76.
Drugs Not Analyzed	None.

Antiparasitic Drugs

Serious Postapproval Risks

Praziquantel	NDA 18-714, approved 12/29/82. Serious label change: addition to the contraindications section that ocular cysticercosis should not be treated because parasite destruction within the eye may cause irreparable lesions.
Sulfadoxine and Pyrimethamine	NDA 18-557, approved 10/28/81. Serious label changes: in the indications and usage section, addition of qualifications for use to those in whom chloroquinine resistance is suspected or for prophylactic use to travelers to areas where chloroquinine-resistant malaria is endemic; addition to the contraindications section that prophylactic use is contraindicated in those with severe renal insufficiency, marked liver parenchymal damage or blood dyscrasia; addition of boxed warning about fatalities from severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, with suggestion for discontinuance at first appearance of skin rash and with other reasons for discontinuance (significant reduction of formed blood elements or occurrence of bacterial or fungal infection) also moved into box; addition to the precautions section under information for patient (at appearance of skin rash, to stop use and seek medical attention, as well as for arthralgia, cough, and shortness of breath), under carcinogenesis, mutagenesis, impairment of fertility (addition of testicular changes in rats, no change in fertility or mating, reduction in pregnancy rate at high doses), and under pregnancy (addition of teratogenic effect as reason for caution in use during pregnancy and addition of warning to women of childbearing potential not to become pregnant); addition to the warnings section of severe reactions causing fatalities (fulminant hepatic necrosis); and addition to the adverse reactions section of toxic epidermal necrolysis and hepatocellular necrosis.

No Serious Postapproval Risks

Niclosamide	NDA 18-669, approved 5/14/82.
Oxamniquine	NDA 18-069, approved 7/23/80.

Drugs Not Analyzed

None.

Oncology Drugs

Serious Postapproval Risks

Carmustine (BCNU)	NDA 17-422, approved 3/7/77. Serious label changes: addition to the boxed warning (1) that bone marrow suppression (thrombocytopenia and leukopenia) is the most toxic effect and that it may contribute to bleeding and overwhelming infections in an already compromised patient and (2) of dose-related pulmonary toxicity when cumulative dose is greater than 1,400 mg/m^2 and addition to the adverse reactions section of acute leukemia and bone marrow dysplasia (with long-term nitrosourea therapy), pulmonary toxicity characterized by pulmonary infiltrates or fibrosis with total doses of 1,400 mg/m^2(but also at lower cumulative doses), with fatal cases reported and repeating of material in boxed warning in regular warnings section along with addition that secondary malignancies may result from long-term use, and that fetal harm can result when administered to a pregnant woman (with recommendation to avoid pregnancy).
Cisplatin	NDA 18-057, approved 12/19/78. Serious label changes: additions to the warnings section of concern about severe irreversible neuropathies when dosage is exceeded (paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation) and addition to the adverse reactions section of vascular toxicities with other antineoplastic agents (possibly including myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, or cerebral arteritis).

Cyclosporine	NDA 50-573, approved 11/14/83. Serious label changes: addition to the warnings section of a concern about syndrome of thrombocytopenia and microangiopathic hemolytic anemia, significant hyperkalemia and hyperuricemia, and convulsions (particularly in combination with high dose methylprednisolone); addition of a warning in bold print about possible anaphylactic reactions (1 in 1,000), requiring continuous observation for 30 minutes following beginning of IV infusion and at frequent intervals thereafter, thought to be the polyoxyethylated castor oil used as the vehicle (with flushing of the face and upper thorax, acute respiratory distress with dyspnea and wheezing, blood pressure changes and tachycardia, with one death reported after respiratory arrest and aspiration pneumonia); and additions to the precautions section that cyclosporine is not to be used with potassium-sparing diuretics because of hyperkalemic effect and under drug interactions of increased plasma levels (from methylprednisolone).
Lomustine	NDA 17-588, approved 8/04/76. Serious label changes: addition of a boxed warning (1) that bone marrow toxicity is cumulative so dosage adjustment should be based on nadir blood counts from prior dose (and that it is the major toxicity and may contribute to bleeding and overwhelming infections in an already compromised patient), (2) for administration by experienced individuals, and (3) for the importance of weekly blood counts and frequency more than every six weeks because of the major toxicity-delayed bone marrow suppression (the latter two were already in the label but moved to the boxed warning); addition to the warnings section that secondary malignancies are associated with long-term use of nitrosoureas and that liver and renal function should be monitored, and under pregnancy, change from safety not established to "can cause fetal harm" and that patient should not become pregnant but if so should be apprized of risk to fetus; addition to the precautions section, under carcinogenicity, of carcinogenic potential from nitrosourea therapy; addition to the adverse reactions section of (rarely) pulmonary toxicity (pulmonary infiltrates or fibrosis) after 6 months of therapy with cumulative doses greater than 1,100 mg/M^2 with corresponding addition to the warnings section that pulmonary toxicity is dose-related; and putting directions for repeat course into bold print in the dosage and administration section.
Tamoxifen Citrate	NDA 17-970, approved 12/30/77.

	Serious label change: revision of discussion in the warnings section on pregnancy category, previously indicating possible oncogenic activity, teratogenicity with evidence of skeletal abnormalities, and effects on reproductive functions, now indicating reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding, with addition of statement that individuals should not become pregnant (along with statement of possible fetal harm, and results of animal studies—effects on reproductive functions expected from antiestrogenic properties, nonteratogenic reversible skeletal changes, a lower incidence of embryo implantation, and a higher incidence of fetal death or retarded in utero growth, and slower learning behavior), and addition of ocular changes at recommended doses (visual disturbances, cataracts, corneal changes, or retinopathy, with uncertain relationship).

No Serious Postapproval Risks

Daunorubicin Hcl	NDA 50-484, approved 12/19/79.
Estramustine Phosphate Sodium	NDA 18-045, approved 12/24/81.
Etoposide	NDA 18-768, approved 11/10/83.
Streptozocin	NDA 50-577, approved 5/7/82.

Drugs Not Analyzed

None.

Radiopharmaceuticals

Serious Postapproval Risks

Gallium Citrate Ga-67	NDA 17-478, approved 5/17/76. Serious label change: the addition to the warnings section about the hazard of the benzyl alcohol content in administration to newborns.
Iohexol	NDA 18-956, approved 12/26/85.

	Serious label changes: the addition of convulsions under intrathecal adverse reactions with iohexol probably involved (as opposed to reactions reported in the literature for other nonionic, water-soluble myelographic media).
Iopamidol	NDA 18-735, approved 12/31/85 Serious label changes: in the adverse reactions section, addition that major motor seizures have been reported since market introduction (as well as, previously stated, in the clinical literature), and in the dosage and administration section, putting into bold print statement about maximum total dose and italicization of statement that, as with other contrast agents, the lowest dose should be used and be carefully individualized, with additional bold statement that minimum dose should be used.
Ioxaglate Meglumine and Ioxaglate Sodium	NDA 18-905, approved 7/26/85. Serious label changes: an addition to the warnings section (with convulsions and death reported rarely for patients with subarachnoid hemorrhage) and a change to the precautions section under selective coronary arteriography (from a suggestion for not using this drug for two weeks following a myocardial infarction to a suggestion for caution in patients with incipient heart failure because of the possibility of aggravating the preexisting condition, with special care regarding dosage in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds).
Metrizamide	NDA 17-982, approved 8/23/78. Serious label changes: addition of contraindications of intrathecal coadministration of corticosteroids, immediate repeat myelography, and lumbar puncture in the presence of infection where bacteremia is likely; in the warnings section, removal of statement about no fatal reactions associated with metrizamide, addition about greater risk following myelography for elderly patients, addition of risk factors associated with major motor seizures, concern about inadvertent intracranial entry because of increased risk of seizure, and avoidance of drugs that lower the seizure threshold; additions to the adverse reactions section of focal or generalized grand mal motor seizures (with incidence of 0.1 to 0.3 percent), an aseptic meningitis syndrome, and generalized angioedema

	with marked dyspnea and stridor (with deaths reported); in the overdosage section, addition that even use of recommended dosage is tantamount to overdosage with incorrect patient management; and in the dosage and administration section, additions that the period for repeat procedures should be at least 48 hours but preferably 5 to 7 days and with a considerable expansion of suggestions for usual patient management.

No Serious Postapproval Risks

Dimercaptosuccinic Acid	NDA 17-944, approved 05/18/82.
Indium In-111 Oxyquinoline	NDA 19-044, approved 12/24/85.
Iodohippurate Sodium I-123	NDA 18-289, approved 12/28/84.
Isosulfan Blue	NDA 18-310, approved 7/29/81.
Pentetate Indium Disodium In-111	NDA 17-707, approved 2/18/82.
Sodium Iodide I-123	NDA 17-630, approved 3/24/76.
Technetium, Tc-99M, Albumin	NDA 17-832, approved 2/23/76.
Technetium, Tc-99M Disofenin	NDA 18-467, approved 3/16/82.
Thallous Chloride Tl 201	NDA 17-806 approved 12/15/77.
Xenon Xe 127	NDA 18-536, approved 10/1/82.
Ytterbium Yb-169 Dtpa	NDA 17-518, approved 3/11/76.

Drugs Not Analyzed

125 I Fibrinogen (Human)	NDA 17-787, approved 6/28/76.
Albumin, Chromated, Cr-51, Serum	NDA 17-835, approved 2/23/76.

Albumin, Iodinated, I-125, Serum	NDA 17-836, approved 2/23/76.
Albumin, Iodinated, I-131, Serum	NDA 17-841, approved 2/23/76.

Anti-Inflammatory Drugs

Serious Postapproval Risks

Auranofin	NDA 18-689, approved 5/24/85. Serious label changes: addition to the precautions section of concern, under hematologic reactions, of aplastic anemia; and addition to the adverse reactions section of (incidence less than 1 percent, probable causal relationship) aplastic anemia, pancytopenia, toxicity, and blood disorders.
Benoxaprofen	NDA 18-250, approved 4/19/82. Serious label changes: in the precautions section, modification of discussion of liver function abnormalities from need for continued monitoring with discontinuance if abnormalities continue to statement that elevations may progress, remain the same, or be transient, with symptoms to be evaluated for severe hepatic reactions (including cholestatic jaundice and fatal hepatitis with renal failure) and of renal function from lower dose in elderly debilitated patients with impaired renal function to lower dose in elderly patients in whom renal function is normally decreased and in whom creatinine levels may not reflect a decrease in renal function; in the adverse reactions section, addition of cholestatic jaundice and aplastic anemia; and in the dosage and administration section, addition of boldface statement for reduced dosage in elderly patients (using half to two thirds the usual dose). (Drug withdrawn for safety reasons, for liver disease causing death.)
Diflunisal	NDA 18-445, approved 4/19/82. Serious label changes: addition to the warnings section of fatalities associated with gastrointestinal bleeding with higher morbidity and mortality in acutely ill patients, the elderly, and patients with hemorrhagic

disorders; additions to the precautions section of a general statement about the possibility of association with Reye syndrome (based on results with acetylsalicylic acid from which diflunisal is derived), of reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome (patients at greatest risk being those with renal or hepatic dysfunction, diabetes mellitus, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of nephrotoxic drugs), and of concern about drug interaction with indomethacin (change from "dose of indomethacin would probably need to be reduced" to "should not be used concomitantly" because associated with fatal gastrointestinal hemorrhage); and additions to the adverse reactions section of erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, dysuria, hematuria, proteinuria, renal impairment (including renal failure), interstitial nephritis, acute anaphylactic reaction with bronchospasm, and an apparent hypersensitivity syndrome (potentially life-threatening, multisymptomed including fever, chills, cutaneous findings, changes in liver function, jaundice, leukopenia, thrombocytopenia, eosinophilia, disseminated intravascular coagulation, renal impairment, adenitis, arthralgia, myalgia, arthritis, malaise, anorexia, and disorientation).

Fenoprofen Calcium

NDA 17-604, approved 3/16/76.

Serious label changes: addition to the warnings section of reports of fatalities from gastrointestinal bleeding and reports of genitourinary problems, including dysuria, cystitis, hematuria, interstitial nephritis and the nephrotic syndrome; additions to the precautions section of reports of acute interstitial nephritis and nephrotic syndrome and severe hepatic reactions, including jaundice and cases of fatal hepatitis; and additions to the adverse reactions section of cholestatic hepatitis, cystitis, hematuria, oliguria, azotemia, anuria, papillary necrosis, interstitial nephritis, nephrosis, thrombocytopenia, hemolytic anemia, aplastic anemia, agranulocytosis, pancytopenia, and hemorrhage.

Meclofenamate Sodium

NDA 18-006, approved 6/25/80.

Serious label changes: addition of concern in the precautions section about renal effects based on reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome and additions to the adverse reactions section of renal failure, neutropenia,

thrombocytopenic purpura, leukopenia, agranulocytosis, hemolytic anemia, eosinophilia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, and serum-sickness-like symptoms.

Naproxen

NDA 17-581, approved 3/11/76.

Serious label changes: addition to the precautions section of a bold, uppercase warning against use with naproxen sodium; additions to the precautions section (of reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome; and severe hepatic reactions, including jaundice and cases of fatal hepatitis); and additions to the adverse reactions section of (less than 1 percent with probable relationship to the drug) interstitial nephritis and nephrotic syndrome.

Piroxicam

NDA 18-147, approved 4/6/82.

Serious label changes: addition to the warnings section of reports of perforation and gastrointestinal bleeding, sometimes severe and, in some instances, fatal; additions to the precautions section (reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome; severe hepatic reactions, including jaundice and cases of fatal hepatitis; dermatological or allergic signs and symptoms suggestive of serum sickness, including arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis; and, under drug interactions, reported interactions with coumarin-type anticoagulants and possible increase in steady-state plasma lithium levels); and additions to the adverse reactions section of (less than 1 percent with probable relationship to the drug) hepatitis, perforation and ulceration, bone marrow depression including aplastic anemia, exfoliative dermatitis, vesiculo bullous reactions, interstitial nephritis, hyperkalemia, papillary necrosis, nephrotic syndrome, renal failure, anaphylaxis, bronchospasm, and serum sickness.

Sulindac

NDA 17-911, approved 9/27/78.

Serious label changes: additions to the warnings section of fatalities from peptic ulceration and gastrointestinal bleeding (associated with patients acutely ill with other conditions, the elderly and patients with hemorrhagic disorders) and of abnormalities in liver tests and severe skin reactions (as evidence of hypersensitivity) in patients with fatalities, hepatitis and jaundice; additions to the precautions section of reports of acute interstitial nephritis (with hematuria, proteinuria, and

occasionally nephrotic syndrome); and additions to the adverse reactions section of erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, thrombocytopenia, leukopenia, agranulocytosis, neutropenia, bone marrow depression (including aplastic anemia), hemolytic anemia, hematuria, proteinuria, crystalluria, hyperkalemia, renal impairment (including renal failure), interstitial nephritis, nephrotic syndrome, hypersensitivity vasculitis, anaphylaxis, and a potentially fatal apparent hypersensitivity syndrome (possibly including fever, chills, rash, other dermatologic reactions, changes in liver function, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leukopenia, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment including renal failure, adenitis, arthralgia, myalgia, fatigue, malaise, hypotension, chest pain, and tachycardia).

Suprofen

NDA 18-217, approved 12/24/85.

Serious label changes: addition to the warnings section of a boxed warning about the abrupt onset of flank pain with generally reversible renal insufficiency (with drug discontinuation and monitoring of renal function for 2 years) and uricosuria shortly after first dose, particularly in patients not adequately hydrated; addition to the indications and usage section of a bold-print limitation of usage (not to be considered as the initial treatment because flank pain accompanied by renal function abnormalities may occur); addition to the precautions section (under information for patient) advising adequate hydration and notification of physician of pain in the back; and addition to the adverse reactions section of (incidence less than 1 percent, probable causal relationship) thrombocytopenia, leukopenia, agranulocytosis, aplastic anemia, bone marrow depression, colitis, and acute flank pain with renal insufficiency. (Drug withdrawn for safety reasons, for flank pain syndrome.)

Tolmetin Sodium

NDA 17-628, approved 3/24/76.

Serious label changes: addition of reports in the precautions section of acute interstitial nephritis with hematuria, proteinuria and occasionally nephrotic syndrome and of severe hepatic reactions, including jaundice and fatal hepatitis, and additions to the adverse reactions section of (less than 1 percent, probable causal relationship to use of the drug) hepatitis, serum sickness, hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis, erythema multiforme, toxic epidermal necrolysis, hematuria, proteinuria, dysuria, and renal failure.

Zomepirac Sodium	NDA 18-236, approved 10/28/80. Serious label changes: addition to the contraindications of a reason (possibly of cross-sensitivity) for not giving Zomax to patients in whom NSAIDs induce bronchospasm, rhinitis, or urticaria; addition of statement in the precautions section that, as with other NSAIDs, anaphylactoid reactions have been reported and that, because of cross-sensitivity among NSAIDs, such reactions may be more likely in patients who have had allergic reactions to these compounds, particularly tolmetin sodium. (Drug withdrawn for safety reasons, because of adverse reactions indicating a suspected, greater than acceptable risk of anaphylactic reactions.)

No Serious Postapproval Risks

Beclomethasone Dipropionate	NDA 17-573, approved 5/12/76.
Dimethyl Sulfoxide	NDA 17-788, approved 4/4/78.
Flunisolide	NDA 18-148, approved 9/24/81.

Drugs Not Analyzed

None.

Respiratory Drugs

Serious Postapproval Risks

None.

No Serious Postapproval Risks

Albuterol	NDA 17-559, approved 5/1/81.
Azatadine Maleate	NDA 17-601, approved 3/29/77.
Bitolterol Mesylate	NDA 18-770, approved 12/28/84.

Clemastine Fumarate	NDA 17-661, approved 2/25/77.
Terfenadine	NDA 18-949, approved 5/8/85.

Drugs Not Analyzed

None.

Surgical Drugs

Serious Postapproval Risks

Chymopapain

NDA 18-663, approved 11/10/82.

Serious label changes: addition to the contraindications section of significant spinal stenosis and other lesions producing spinal motor or sensory dysfunction (formerly, just cauda equina lesion, now only an example); changes in the warnings section: (1) modification of boxed warning and main warnings section changing rate of occurrence of anaphylaxis from 1 percent to 0.5 percent (with additional information based on 71,000 patients showing difference in rate between patients receiving local or general anesthesia, by sex and noting a higher incidence in black females) and adding warnings about (a) (i) paraplegia/paraparesis, central nervous system hemorrhage and seizures (subarachnoid and intracerebral), and other serious neurologic adverse events (1 in 2,000, with causal relationship when properly injected not established, but suggesting needle trauma or injection of chymopapain and contrast media into the spinal fluid as causes in some cases), including the addition of foot drop (also added to the adverse reactions section); (ii) acute transverse myelitis and acute transverse myelopathy (1 in 18,000, higher than rate in medical literature, although a cause and effect relationship has not been established, characterized by delayed onset—2 to 3 weeks—of paraplegia or paraparesis without prior signs or symptoms) (also added to the adverse reactions section); and (iii) the co-occurrence of neurologic events, warning about prior surgery and the relationship between extensive, severe, or fatal CNS hemorrhage and a history of hypertension, known or suspected cerebrovascular anomaly, previous cerebrovascular accident, or a strong family history of cerebrovascular anomaly (recommending in this section as well as the precautions section selection of such patients only after careful

	consideration); (b) toxicity when injected intrathecally (along with radiopaque contrast media used for discography), requiring great care to ensure that the dura is not penetrated and that neither chymopapain nor contrast media enter the subarachnoid space (with the possibility that if chymopapain is inadvertently administered intrathecally, disruption of the capillaries may result in intrathecal bleeding); (c) the inadvisability of concomitant discography or injection into more than one disk; and (d) using local anesthesia whenever possible; (2) in the main warnings section, addition of several notes concerning the occurrence of serious neurologic adverse events along with italicized recommendations corresponding to the particular note: (a) co-occurrence of events with discography, with less serious events when no discography (recommending that discography not be performed at same time), (b) concerning injection into two or more disk spaces (recommending limiting to one disc unless more than one is definitively related to signs and symptoms), (c) regarding use of local versus general anesthesia (recommending local whenever possible), and (3) italicizing warning about toxicity when injected intrathecally; and in the precautions section, additions in italics (a) under pretreatment, of necessity for having an open intravenous line in place for possible treatment of anaphylaxis and (b) under procedure, that if x-ray equipment for needle placement not available then chemonucleoysis should not be performed.
Intravenous Fat Emulsion	NDA 18-203, approved 5/16/79. Serious label change: the addition of a boxed warning about deaths in preterm infants who have poor clearance of intravenous fat emulsion with the possibility of interavenous fat overload.
No Serious Postapproval Risks	None.
Drugs Not Analyzed	None.

Anesthesia Drugs

Serious Postapproval Risks

Atracurium Besylate

NDA 18-831, approved 11/23/83.

Serious label changes: addition to the adverse reactions section of allergic reactions (anaphylactoid responses) that were severe in some cases (e.g., cardiac arrest) and addition of a multiple dose vial containing benzyl alcohol as a preservative that may cause "gasping syndrome" death in neonates.

Etidocaine Hydrochloride

NDA 17-751, approved 8/30/76.

Serious label changes: in the warnings section, additional uppercase concern about use by qualified personnel with appropriate resuscitative equipment and drugs, with the warning that delay may result in toxicity, underventilation, acidosis, cardiac arrest, and death, and addition of warning about sodium metabisulfite which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes; additions to the precautions section of (1) discussion on labor and delivery, changing from use in obstetrical analgesia by the peridural route revealing no evidence of effects on fetus to local anesthetics causing varying degrees of maternal, fetal, and neonatal toxicity involving the central nervous system, peripheral vascular tone, and cardiac function, including maternal hypotension, diminished muscle strength and tone in the neonate for the first day or two of life, profound motor block when used epidurally (hence not recommended for use in normal delivery), and when used paracervically, fetal bradycardia in 20-30 percent of patients (possibly associated with fetal acidosis), seizures (possibly from unintended fetal intracranial injection), and maternal convulsions and cardiovascular collapse when used in early pregnancy (thus militating against use in paracervical block); (2) concern about syringe aspirations before and during each supplemental injection, with test dose to be used to monitor for CNS and cardiovascular toxicity, to insure against unintended intravascular injection; (3) concern about use in areas of compromised blood supply of possible exaggerated vasoconstrictor response (ischemic injury or necrosis) in patients with peripheral or hypertensive vascular disease; and (4) precaution for careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness for early

	signs of CNS toxicity; and removal from the dosage and administration section of dosage recommendations for percutaneous infiltration and vaginal obstetrical and gynecologic procedures.
Etomidate	NDA 18-227, approved 9/7/82. Serious label changes: addition to the warnings section in uppercase that prolonged infusion should not be used because of the suppression of cortisol and aldosterone; addition to the precautions section of concern about plasma cortisol levels, with suggestion for consideration of exogenous replacement for patients undergoing severe stress; and addition to the clinical pharmacology section of reduced cortisol plasma levels unresponsive to ACTH administration and that volume of distribution and elimination half-life are double in patients with cirrhosis and esophageal varices.

No Serious Postapproval Risks

Sufentanil Citrate	NDA 19-050, approved 5/4/84.
Vecuronium Bromide	NDA 18-776, approved 4/30/84.

Drugs Not Analyzed

Isoflurane	NDA 17-624, approved 12/18/79.

Renal Drugs

Serious Postapproval Risks

None.

No Serious Postapproval Risks

None.

Drugs Not Analyzed

Acetohydroxamic Acid	NDA 18-749, approved 5/31/83.

Cardiac (II) Drugs

Serious Postapproval Risks

None.

No Serious Postapproval Risks

Trientine Hydrochloride	NDA 19-194, approved 11/8/85.

Drugs Not Analyzed

None.

Gastrointestinal Drugs

Serious Postapproval Risks

Cimetidine	NDA 17-920, approved 8/16/77.

Serious label changes: additions to the precautions section of concern about (1) rare instances of cardiac arrhythmias and hypotension following rapid administration by intravenous bolus, the possible presence of a gastric malignancy despite symptomatic response, and reversible confusional states predominantly in severely ill patients (with additions to the adverse reactions section of reversible confusional states, including mental confusion, agitation, psychosis, depression, anxiety, hallucinations, and disorientation, usually in severely ill patients), and (2) drug interactions, with effects from reduction in hepatic metabolism on warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline, and metronidazole, suggesting adjustment particularly in patients with renal or hepatic impairment.

Difenoxin and Atropine	NDA 17-744, approved 7/14/78. Serious label changes: in the warnings section, change of statements to uppercase that the drug is not recommended for children under 2 years of age, that overdosage may result in severe respiratory depression and coma, possibly leading to permanent brain damage or death, and that fluid and electrolyte balance may be severely affected; in the precautions section, addition in uppercase cautioning adherence to recommended dosage and keeping the drug out of reach of children because of possibility of overdosage resulting in severe, even fatal, respiratory depression, change under the nursing mothers subsection from effects may be evident because excreted to decision should be made which to discontinue because of serious adverse reactions, and under pediatric use putting statements about safety and effectiveness under 12 and contraindication under 2 into uppercase; in the adverse reactions section, addition of uppercase statement to use a child-resistant container because of overdosage resulting in severe respiratory depression and coma; and in the dosage and administration section, addition of uppercase statement to treat all possible overdosage as serious and putting into uppercase statement about maintaining continuous observation in hospital for 48 hours.
Lactulose	NDA 17-657, approved 3/25/76. Serious label changes: addition of warnings section, with concern about patients who may undergo electrocautery procedures during proctoscopy or colonoscopy because of potential explosive reaction from accumulation of H_2 gas, suggesting that patients should have a thorough bowel cleansing with a nonfermentable solution.
Metoclopramide	NDA 17-862, approved 2/7/79. Serious label changes: additions to the warnings section about depression (with or without prior history, with mild, severe, suicidal ideation, and suicide symptoms), extrapyramidal symptoms (more frequent at higher doses used for new indications), and tardive dyskinesia (potentially irreversible with an increased likelihood along with duration and total cumulative dose, possibly masked) and additions to the adverse reactions section of confusion, depression, mental depression with suicidal ideation, convulsive seizures (isolated without clearcut relationship), hallucinations (rarely), additional symptoms under extrapyramidal reactions (opisthontonus, and rarely stridor and dyspnea), and tardive dyskinesia (characterized by involuntary movements

	of the tongue, face, mouth, or jaw and that may be choreoathetotic in appearance).
No Serious Postapproval Risks	
Bentiromide	NDA 18-366, approved 12/29/83.
Ceruletide	NDA 18-296, approved 12/24/81.
Chenodiol	NDA 18-513, approved 7/28/83.
Loperamide Hcl	NDA 17-694, approved 12/28/76.
Monooctanoin	NDA 19-368, approved 10/29/85.
Ranitidine Hydrochloride	NDA 18-703 approved 6/9/83.
Secretin	NDA 18-290, approved 5/29/81.
Sincalide	NDA 17-697, approved 7/21/76.
Sucralfate	NDA 18-333, approved 10/31/81.
Drugs Not Analyzed	None.

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Statistical Analysis of FDA Drug Data

We used logistic regression analysis and log-linear modeling of the FDA drug data set to examine the association between the occurrence of serious postapproval risk for a drug and selected characteristics related to the drug approval process. We used logistic regression analysis since the dependent variable—that is, whether or not a drug had serious postapproval risks—is a categorical variable. The logistic regression analysis permitted us to screen a larger set of variables and to focus on only those that appeared to be statistically significant. The use of bivariate models, the full main effects model considering all independent variables used in the study, and the reduced main effects model were described in chapter 3 and portrayed in table 3.2.[1] The reduced main effects model included only the variables use with children, appearance on the MART list, and period of approval.

Log-linear modeling involves the comparison of a hierarchy of related models examining all possible interactions among the data. The comparison of these models allows a statistical test of whether specific factors have significant relationships with the dependent variable and how they interact. Expected frequencies derived from models that include statistically significant effects can be used to produce estimates of the magnitude and direction of the relationships (Goodman, 1978). Such estimates can take a variety of forms; for our analyses, we chose odds and odds ratios.

Odds indicate the tendency of a given subgroup of the population under study, as defined by one variable in the analysis, to assume one value of a specified variable rather than another. Different subgroups can be compared by observing the ratio of their odds. Where there are no significant differences between two groups, their odds are equal, and the odds ratio between them is 1.0. In other words, there is no effect on the dependent variable associated with variation in the variables that distinguish the two subsets. The greater the divergence of the odds ratio from unity, the larger the magnitude of the effect. The results summarized in table 3.2 for the bivariate and full main effects models provide odds ratios for important therapeutic gain, modest therapeutic gain, foreign marketing experience, month of approval, and years taken for approval. Although these odds ratios differ from 1.0, the analysis indicates that the differences are not significant. In other words, the lack of statistical significance associated with them indicates that the

[1]The variable for therapeutic gain is trichotomous. To facilitate analysis of this variable using log-linear modeling, two dummy variables (one representing important therapeutic gain and the other representing modest therapeutic gain) were used. This approach is equivalent to direct consideration of the trichotomous variable but is computationally simpler.

probability is greater than 1 in 10 that the "true" value of these odds ratios is 1.0, indicating no relationship.

The log-linear modeling we performed for our study involved the "logit" mode of analysis, which allows an unconstrained association between all the independent variables but varies their association with a predetermined dependent variable. In this mode, a hierarchy of related models is set up, ranging from fairly simple to relatively complex. The simplest models posit that none, one, or only a few of the independent variables in the cross-classifications have a main effect on the dependent variable. Complex models can include interactions between the factors that affect the dependent variable.

A computer program generates a set of expected frequencies for each model; these are then contrasted with the observed frequencies—that is, the data being analyzed—and the discrepancy between the two is measured by means of a "likelihood ratio chi-square." By systematically comparing the likelihood ratio chi-square values for models of increasing complexity, one can select a model that includes only the variables that have a statistically significant relationship to the dependent variable, after controlling for the association of the other variables in the equation with one another and with the dependent variable. In general, one seeks the simplest model that fits the data adequately and that cannot be significantly improved (in terms of a decrease in likelihood ratio chi-square values relative to degrees of freedom) by the addition or subtraction of another variable.

Once this "preferred" model has been selected, odds and odds ratios are calculated from the expected frequencies that it generates. The resultant estimate of the effect of a given variable is a net effect. It is determined after the association of this variable with all the other independent variables has been taken into account, as well as all other associations of these variables with the model's dependent variable.

Using our data set, we represented the dependent variable using 0 if the drug did not have a serious postapproval risk or 1 if the drug did have a serious postapproval risk. We represented the other variables as indicated in table 3.1 in chapter 3. After running the logistic regression, we determined that we focus more detailed analysis on three variables: use with children, appearance on the MART list, and period of approval. The frequencies for these variables are shown in table 3.3 in chapter 3. We examined the hierarchical models for these variables, with the results shown in table IV.1.

Table IV.1: Confirmation of Preferred Model for Log-Linear Analysis of Factors Associated With Serious Postapproval Risk

Model	Marginals fitted[a]	Likelihood ratio chi-square(L^2)	df	p
1	[CMP] [R]	58.73	7	<0.0001
2	[CMP] [CR]	52.91	6	<0.0001
3	[CMP] [MR]	15.71	6	0.0154
4	[CMP] [PR]	55.96	6	<0.0001
5	[CMP] [CR] [MR]	10.11	5	0.0722
6	[CMP] [CR] [PR]	50.95	5	<0.0001
7	[CMP] [MR] [PR]	5.35	5	0.3751
8	[CMP] [CR] [MR] [PR]	1.23	4	0.8730
9	[CMP] [CMR]	10.03	4	0.0399
10	[CMP] [CPR]	50.94	4	0.0001
11	[CMP] [MPR]	4.92	4	0.2961
12	[CMP] [CMR] [PR]	1.17	3	0.7592
13	[CMP] [CPR] [MR]	1.11	3	0.7748
14	[CMP] [MPR] [CR]	0.86	3	0.8360
15	[CMP] [CMR] [CPR]	1.09	2	0.5788
16	[CMP] [CMR] [MPR]	0.82	2	0.6645
17	[CMP] [CPR] [MPR]	0.76	2	0.6839
18	[CMP] [CMR] [CPR] [MPR]	0.75	1	0.3857

[a]C = use with children; M = appearance on MART list; P = period of approval; R = postapproval risk.

All the models in table IV.1 can be described, following Goodman's notation, in terms of the underlying marginals of the four-way table that they fit (that is, table 3.3 in chapter 3). Model 1 in table IV.1 fits the [CMP] marginal (or the three-way marginal to allow the three process-related variables to be associated with one another) and the [R] marginal (or the one-way marginal for postapproval risk) and nothing else. As such, it is the logit-specified model of independence that asserts that the presence of postapproval risks is unrelated to any of the three variables in the table. Such a model clearly does not provide an acceptable fit to the data, given that the likelihood-ratio chi-square of 58.73 has, with 7 degrees of freedom, a probability of less than 0.0001.

Moreover, model 1 is improved upon by all the other models, which by fitting various combinations of direct effects ([CR], [MR], and [PR] marginals) or higher order interactions ([CMR], [CPR], and [MPR] marginals), allows postapproval risks to be associated in various ways with the three other variables in the table.

The table indicates that the preferred model is model 8, the "main effects" model. This means that the interaction of each of the three independent variables with the dependent variable of postapproval risk is necessary to explain the variation shown in table 3.3 of chapter 3 but that no more complex variation (involving higher-order interactions among the variables) significantly improves the fit of the model to the data. This is confirmed by contrasting the models, examining the difference in the likelihood ratio chi-square, as shown in table IV.2. That all of the associations in the preferred model are significant is demonstrated by the fact that model 8 fits the data significantly better than any one model 5 through 7, which drop one of these pairwise associations at a time.[2] Finally, it is clear that only these direct effects are needed to describe the variation in postapproval risks, since none of the models 12 through 14, which each allow one interaction term, improve significantly upon model 8.

[2]In other words, the difference in likelihood-ratio chi-square for each comparison as shown in table IV.2 is statistically significant.

Table IV.2: Contrast of Models and Examination of Effects to Determine Significance

Models compared	Effect tested[a]	Difference in degrees of freedom	Likelihood ratio chi-square difference
1-2	CR	1	5.82**
1-3	MR	1	43.02***
1-4	PR	1	2.77*
2-5	MR	1	42.80***
2-6	PR	1	1.96
3-5	CR	1	5.60**
3-7	PR	1	10.36***
4-6	CR	1	5.01**
4-7	MR	1	50.61***
5-8	PR	1	8.88***
6-8	MR	1	49.72***
7-8	CR	1	4.12**
5-9	CMR	1	0.08
6-10	CPR	1	0.01
7-11	MPR	1	0.43
8-12	CMR	1	0.06
8-13	CPR	1	0.12
8-14	MPR	1	0.37
9-12	PR	1	8.86***
10-13	MR	1	49.83***
11-14	CR	1	4.06**
12-15	CPR	1	0.08
12-16	MPR	1	0.35
13-15	CMR	1	0.02
13-17	MPR	1	0.35
14-16	CMR	1	0.04
14-17	CPR	1	0.10
15-18	MPR	1	0.34
16-18	CPR	1	0.07
17-18	CMR	1	0.01

* $p < 0.10$.

** $p < 0.05$.

*** $p < 0.01$.

[a]C = use with children; M = appearance on MART list; P = period of approval; R = postapproval risk.

As a result of this analysis, the preferred model is the main effects model (model 8 in table IV.1). It is used to generate the expected frequencies, odds, and odds ratios presented in table 3.4 in chapter 3.

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of Inspector General

Washington, D.C. 20201

DEC 22 1989

Mr. Lawrence H. Thompson
Assistant Comptroller General
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Thompson:

Enclosed are the Department's comments on your draft report, "FDA Drug Review: Postapproval Risks, 1976 - 1985." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE (GAO) DRAFT REPORT, "FDA DRUG REVIEW: POSTAPPROVAL RISKS, 1976 - 1985," NOVEMBER 1989

General Comments

See comment 1.

While the question raised by GAO -- namely, whether any characteristics of the review process could contribute to serious risks being overlooked during the review -- is a valid and serious question, we find the report is not methodologically sound, does not present a clear objective, is not accurate in many details, does not show insight into new drug development and review, and is very elementary in concept. We are concerned that this report, if issued without significant revisions and corrections, will unnecessarily alarm consumers, causing some to reject the use of lifesaving drugs out of fear of adverse events that may occur only in extremely rare instances. Moreover, the tone of the Executive Summary overdramatizes the content of the text and thereby contributes to creating a misleading impression of the drug review process. Yet the report finds no fault with the process. We recommend that the tone and conclusiveness of the Executive Summary conform more closely with the preliminary research orientation of the study itself. The report characterizes itself as providing only an initial understanding of the factors underlying serious approval risks and readily concedes the need to examine the value and limitations of the GAO analyses.

See comment 2.

If the point of the GAO study is to relate some aspect of the review process to a failure to detect postapproval risks, it will be possible to detect such a linkage, if one exists, only where the process could have detected the risk. If the risk has nothing to do with the review process (e.g., it is too rare to be detected, it is unrelated to the particular drug but related to the class) then all processes, good or bad, will fail to detect it and no distinction can be made.

See comment 3.

The GAO report chose a definition of serious postapproval risk that included class labeling changes (e.g., gastric bleeding and ulcer warnings for Nonsteroidal Anti-inflammatory Drugs; warnings on all parenterals and aerosols containing sulfites) and rare events that could not possibly have been identified in the premarketing process. This yields a large number of such risks but makes it impossible to relate the review process to the discovery of postapproval risk.

See comment 4.

A review of some of the specific drugs cited in the report reveals that of the 17 cardiac drugs, there are only two (disopyramide and flecainide) that developed a non-rare, use-changing postapproval risk rather than the 12 found by the GAO to have such risks. Of the 12 identified by GAO, six do not represent new adverse events and four represent additions to

labeling of rare events or results of studies in a new population. Similar peculiarities of designation appear for the antihypertensive/renal drugs. Captopril, for example, is identified as a drug with a postapproval risk, but in fact, the label change cited was made at the time when captopril's "second-line" status was being eliminated, i.e., when it was considered safer than it had been. Of the 32 drugs in the two classes, cardiac drugs and antihypertensive/renal drugs, only three met a reasonable test for developing a new postapproval risk, a rate of less than 10 percent.

See comment 5.

Rare serious events often have little impact on use of the drug. Equally, perhaps more important, they cannot, by definition, be identified in clinical studies, even if the studies were many times larger than current clinical studies. If the drug development process is inherently incapable of detecting these events, the specific process used to review a particular drug cannot possibly be relevant to the likelihood that such events will be discovered postapproval.

See comment 6.

It is important also to realize that some labeling changes reflect not new information about a drug but rather new attitudes, new availability of alternative treatment, or new syntheses of data from many sources and do not represent a response to specific information about a drug. For example, in the case of amrinone, the labeling change reflected not data on amrinone but a generic statement regarding sulfites.

See comment 7.

The report incorrectly portrays the drug review process as one of "trade-offs" with respect to thoroughness of reviews and recommends refinements to such a "trade-off" scheme. The suggestion that FDA controls the level of scrutiny of the data in accordance with some external assessment, i.e., that we sometimes decide not to do an extensive review, is not correct. While FDA may accept less data in some cases, if the gain is great and the disease devastating (oncologic drugs, AIDS drugs) or if the patient population is very small (orphan drugs), those are explicit decisions made in accordance with FDA regulations, not "trade-offs" affecting the extensiveness of review. For example, the suggestion that drugs intended for use with children would undergo a more intensive review than other drugs reveals a misunderstanding of the purpose for reviewing drugs and not being familiar with the contents of the New Drug Applications (NDA) for which labeling was reviewed for this report. It is very unusual to have a proposed pediatric claim in an NDA, yet in the report this category includes 57 drugs. Moreover, the report found no relation of postapproval problems to therapeutic classification A or B, which would indicate that "trade-offs" do not occur.

See comment 8.

The draft report does not discuss the benefits to be gained by the use of drugs, including those with severe risks. Many drugs have saved lives and improved the quality of life for millions of

people. Some of the drugs that have had postapproval identification of risks are also the only available treatment, the best available treatment, or second line treatment for use when other drugs have failed. By not looking at both benefits and risks--as FDA must do--the report misleads readers to the conclusion that the drug review process is inadequate, yet it does not provide sufficient information to reach any conclusions about the adequacy of the existing process.

See comment 9.

We also note that despite the many appendices, crucial data were not provided in the report. Specifically, there is no listing of the drugs involved in the study showing whether they had such characteristics as review for pediatric use, foreign marketing, or modest therapeutic gain, and no listing of approval times. Therefore, the analyses in chapter 3 cannot be verified. One of the report's primary contentions is that drugs with shorter NDA review times have greater likelihood of serious postapproval risks. Yet, in the regression analysis, it appears that the result for the review time variable is not statistically significant. If the regression results for that variable are indeed not statistically significant, then it seems that the conclusion has not been adequately supported. Other deficiencies in this area are:

- The R-squared statistic is not presented.
- The statistical significance of most of the independent variables is not mentioned, implying that they are not statistically significant. Statistical significance should be explicitly presented for each variable.
- It is not apparent from the report that residuals of the regressions were examined.
- The report does not indicate that correlations were run on the independent variables. Running these correlations is important and the results should be mentioned in the report. (The extent that the independent variables are correlated with each other could affect the validity of the regression results.)
- The inclusion of the Monitored Adverse Reaction Tracking report variable is inappropriate in the regression equation since this variable might be a function of all the other independent variables.

Because of time constraints, the above comments represent only a partial review of this research. Many persons who would be expected to provide in-depth reviews were unable to do so. A true peer review of the research would require considerably more time and significant interaction with the researchers than the Department has been given. We will be happy to discuss this further with GAO.

GAO Recommendation

GAO recommends that FDA make further efforts to characterize postapproval risks for new chemical entities as the basis for making decisions concerning trade-offs affecting the extensiveness of review that is appropriate before a drug is marketed. The number of drugs for which serious postapproval risks were identified raises several questions about the level of overall safety: (1) what information about the safety of a drug is unknown at the time of approval (especially for indications which FDA has not approved but for which physicians are likely to prescribe the drug); (2) what are the uncertainties which give rise to the postapproval risks; and (3) whether these uncertainties are inherent in the development of a drug or are controllable by FDA to some extent. These questions should be addressed by FDA.

Department Comment

See comment 10.

We do not concur. In our view, the Federal Food, Drug, and Cosmetic Act does not direct that the "extensiveness of review" vary according to the circumstances of an individual application. While FDA may accept less data in some cases, if the gain is great and the disease devastating, or if the patient population is very small, those cases require explicit decisions, not prereview "trade offs."

Furthermore, the recommendation presupposes that FDA can, in some undefined, vague way, anticipate the unknown and make decisions about the approvability of drugs based upon such anticipatory judgments. We do not believe this is either possible or desirable, and conclude that the preliminary research effort presented in this report is insufficient to support action on this recommendation.

The following are GAO's comments on the Department of Health and Human Services' letter dated December 22, 1989.

GAO Comments

1. We do not agree with HHS's characterization of the report (methodologically unsound, lacking insight into the drug review process, inaccurate, and so on), primarily because HHS incorrectly views the report as attempting to analyze the drug review process. This is not the intent, as stated in many places in the report. The intent is simply to describe the occurrence of serious postapproval risks, without ascribing their occurrence to any cause at this time. We emphasize here that we do not ascribe the serious postapproval risks to flaws in the drug development and approval process; we have not yet analyzed that process.

We have revised the report in several places in an effort to avoid misunderstandings about what we did and what we found.

2. We agree with HHS's comment that a link between serious postapproval risks and the drug review process will be discoverable only where the review process could have detected the risk. Again, we state that analysis of the process was not the intent of the present study.

3. Our intent in defining serious postapproval risks was not to limit consideration only to those which could have been identified before approval. We believe it is important to identify the extent of risk unknown at the time of drug approval irrespective of the source of that risk. (See pages 16-18.)

4. Our criteria for serious postapproval risks was not limited to "nonrare, use-changing," and "new" adverse reactions. The criteria focused on label changes that represented new adverse reactions or a new appreciation of previously available information. The criteria judged the extensiveness of the label changes and the severity of the underlying adverse reactions, not their frequency or rarity. The criteria could include "results of studies in a new population," although we excluded new populations arising from new indications for a drug. HHS's comments further assess the significance of the postapproval risks for the cardiac and antihypertensive-renal drug classes. We do not challenge these assessments, but they do not change our identification of these drugs as having serious postapproval risks. (See pages 19-21 and 27-29.)

5. We agree that the drug development process can and must accept the possibility that rare serious adverse reactions will not be identified

before approval. We also agree that the specific process used to review a particular drug with rare serious postapproval risks is not likely to be relevant to predicting postapproval risks. However, it is prudent to be open to the possibility that some preapproval findings are predictive of these risks; we will consider this possibility more fully in our later study.

6. We agree with HHS's comment. We discussed these types of labeling changes and pointed out that for specific drugs these types of changes were considered to represent serious postapproval risks. (See pages 28-29.)

7. We have clarified various portions of the report that discuss "trade-offs." The approval of a drug is based on an overall assessment of its benefits and risks. Every drug has risks and these are traded off against its benefits. Although there may be some disagreement among experts for a small number of drugs as to whether their benefits outweigh their risks, a judgment must be made at the end of the review process. We do not address this issue in this report.

Examples of such trade-offs come in the assessment of drugs for which the gain is great and the disease is devastating (for example, oncologic and AIDS drugs) or the patient population is small (orphan drugs), where FDA may accept fewer data. However much FDA's actions are in accord with regulations, and we did not look at that issue, it is still proper to regard the agency's decisions as reflecting trade-offs between a drug's benefits and risks.

Clinical studies can never completely identify the precise extent of all risks associated with a drug. At some point, FDA reviewers must necessarily accept the limitations of the data at hand. We believe that this trade-off may be informed by a greater understanding of the full range of postapproval risks.

With respect to drugs intended for use with children, we presented the hypothesis that they would undergo a greater intensity of review and, hence, would have fewer serious postapproval risks. We did not examine the review process to identify what such "greater intensity" might entail but simply examined drugs marked as such by FDA's Centerwide Oracle Management Information System. We did not verify that this was a meaningful classification but relied on FDA's data for this purpose. Our finding that these drugs were twice as likely to have serious postapproval risks as drugs not characterized as such raises questions. The

first question that should be examined is the meaningfulness of FDA's classification. Then, if the classification is accurate, the most important question would be why these drugs are more likely to have serious post-approval risks. (See pages 44-45 and 48-50.)

8. A full assessment of all benefits and risks for the drugs was beyond the scope of our study. We do not believe that our examination of serious postapproval risks should lead to the conclusion that the drug review process is inadequate. We agree that we have not provided sufficient information to reach any conclusions about its adequacy; as stated before, this is not the intent of this report.

9. There are simply too many data to have included them all or even the data necessary to replicate our analyses. However, computer files of all quantitative data and all the label analyses are available upon request.

We have revised the presentation of our statistical analyses in chapter 3 to clarify our use of log-linear modeling. In particular, we have lessened our emphasis on logistic regression; this change shows that most of what HHS regards as deficiencies are not relevant to our analysis. (See pages 55-56 for further elaboration of our response to HHS's concerns.)

10. We have clarified our recommendation to indicate more specifically that FDA should replicate the study we have performed, bringing to bear its greater familiarity with the drugs and their characteristics. (See chapter 4, pages 57-58, for further details.)

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Glossary

Agonist	A drug possessing affinity and intrinsic activity capable of combining with receptors to initiate drug actions.
Agranulocytosis	Acute condition characterized by pronounced leukopenia with great reduction in the number of polymorphonuclear leukocytes.
Anaphylaxis	Increased susceptibility to a foreign protein resulting from previous exposure to it.
Angiotensin-Converting Enzyme	An enzyme that produces angiotensin, a potent agent that produces vasoconstriction and a rise in blood pressure and the most powerful stimulus for production and release of aldosterone.
Aplastic Anemia	Anemia characterized by a greatly decreased formation of red blood cells and hemoglobin.
Arrhythmia	Irregularity of the heart beat.
Bolus Injection	A rapid injection of the full amount of a dose.
Chemonucleolysis	The enzymatic dissolution of the nucleus pulposus (the soft central portion of the intervertebral disk) in the treatment of disk lesions.
Cholestasis	An arrest in the flow of fluids secreted by the liver.
Discography	Radiographic visualization of intervertebral disk space by injection of contrast media.
Dyscrasia	A morbid general state resulting from the presence of abnormal material in the blood.

Dysplasia	Abnormal tissue development.
Encephalopathy	Any disease of the brain.
Erythema Multiforme	An acute eruption of discolored spots and small, circumscribed skin elevations (solid or containing serum or liquid), presenting a multiform appearance, arising from allergic, seasonal, or drug sensitivity, possibly with a fatal termination.
Hematuria	Any condition in which the urine contains blood or red blood cells.
Hemolytic Anemia	Any anemia resulting from abnormal destruction of mature red blood cells.
Hypersensitivity	Allergy; the state of induced sensitivity.
Hypertension	High arterial blood pressure.
Hypotension	Subnormal arterial blood pressure.
Interstitial Nephritis	An inflammation of the kidneys in which the interstitial connective tissue is chiefly affected.
Ischemia	Local anemia from mechanical obstruction (mainly arterial narrowing) to the blood supply.
Leukopenia	Any situation in which the total number of leukocytes in the circulating blood is less than normal.

Nephrotic Syndrome	A clinical state characterized by edema, the presence of albumin in the urine, decreased plasma albumin, and increased permeability of blood vessels in the kidney.
Neuropathy	Any diseased condition of the nervous system or a disease affecting the cranial or spinal nerves.
Neutropenia	The presence of abnormally small numbers of neutrophils in the circulating blood.
Pharmacokinetics	Movements of drugs within biological systems, as affected by uptake, distribution, elimination, and biotransformation.
Proteinuria	The presence of urinary protein in concentrations greater than normal.
Prothrombin	An enzyme present in the blood and essential for coagulation of the blood.
Pseudotumor Cerebri	An unexplained rise in the pressure of the cerebrospinal fluid.
Stevens-Johnson Syndrome	An eruption of blisters, which may be extensive, involving the mucous membranes and large areas of the body, with serious subjective symptoms and possibly a fatal termination.
Thrombocytopenia	A condition in which there is an abnormally small number of platelets in the circulating blood.
Thrombotic Microangiopathy	Thrombosis within small blood vessels.

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