Evaluating Patient Package Inserts: Report of a Study (1979)

Pages
94

Size
7 x 10

ISBN
0309333539

Institute of Medicine

EVALUATING PATIENT PACKAGE INSERTS

Report of a study

by a committee of the

INSTITUTE OF MEDICINE

August 1979

Supported by the Food and Drug Administration
Contract No. 282-78-0163-EJM

National Academy of Sciences

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Publication IOM 79-05

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ACKNOWLEDGEMENTS

This report is the outcome of a most interesting and enjoyable mutual effort by an IOM committee and staff. The preparation of the report was facilitated by the cooperation of a number of people and organizations who provided information about their activities. Investigators at several universities and other institutions generously provided the committee with copies of unpublished papers, many of which are cited in the bibliography. We are most grateful for their interest and assistance.

The contributions of several people deserve specific acknowledgement. Louis Morris, Ph.D., of the Food and Drug Administration provided extensive bibliographic information that greatly assisted in the literature review that appears in the report. Professor Richard Merrill of the University of Virginia Law School reviewed a preliminary draft of the report and made valuable suggestions regarding the discussion of legal issues and the history of drug regulation in the United States. Linda K. Demlo, Ph.D., in her capacity as Director of the Division of Health Care Services at the Institute of Medicine, offered useful criticism and suggestions at several stages of the project. A word of special thanks to Mrs. Jean Donnelly for her careful, patient, and cheerful handling of multiple drafts and the preparation of the final manuscript.

Bradford H. Gray, Ph.D.
Study Director

Introduction and Summary

The Food and Drug Administration (FDA) has proposed* to require that printed information be dispensed with prescription drugs to inform patients about the drug, its purpose and proper use, its risks, and necessary precautions. This report presents research approaches to evaluate the effects of such governmental regulatory action. The written information provided to patients with pharmaceuticals has come to be known as a "patient package insert" (PPI) whether or not it literally is distributed in the manner that the term suggests. Similar materials have accompanied over-the-counter (non-prescription) medications for many years, but only within the past decade has FDA begun to require the distribution of PPIs with certain prescription drugs, such as oral contraceptives and estrogens. The prospect of PPIs being required more generally has elicited predictions of a wide variety of both beneficial and harmful effects regarding patients' responses, the doctor-patient relationship, prescribing patterns, and the health care system.

Governmental regulation of the labeling of drugs has a history of more than a half-century, dating from efforts under the original Pure Food and Drugs Act of 1906 to prohibit fraudulent claims and deceptive statements on the labels of such drug products as a headache mixture, called Cuforhedake Brane-Fude, "male-weakness" remedies such as Sporty Days Invigorator, and Dr. Johnson's Mild Combination Treatment for Cancer (Young, 1970).

Although the Food, Drug, and Cosmetic Act of 1938 substantially expanded federal labeling requirements for drugs--labels were to include directions for use, indications, and contraindications--FDA's subsequent regulations exempted prescription drugs, as dispensed, from the labeling

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* FDA's formal proposal of "patient labeling requirements" for prescription drug products was published in the Federal Register July 6, 1979, but the agency's general intention to issue such requirements has been widely known for several years. This study was undertaken in anticipation of this regulatory action by FDA, and it addresses questions of evaluation. The deliberations of the study committee were largely completed prior to the announcement of FDA's proposed rules, and this report does not comment specifically on them.

requirement on the condition that manufacturers would provide detailed information to physicians. In 1952 this regulation was codified by Congress in what is now Section 503(b) of the present Act. Providing important information to the patient about the drug was regarded as the responsibility of the practitioner, rather than the manufacturer. This view was consistent with the concept of the prescription drug, which was defined in part by its being unsafe unless administered under the supervision of a licensed practitioner. Thus, a paradox developed, in which substantial labeling information was provided to patients with over-the-counter medications, but drugs that were potentially more hazardous and therefore were available only by prescription had labeling for patients that included only such basic information as the name of the drug, dosage instructions, and the names of the pharmacy and prescribing physician.

FDA first required wider drug labeling information for a prescription drug in 1968 to warn patients against improper use of isoproterenol inhalators, which could produce an effect (bronchoconstriction) opposite to the effect intended. Since then, PPIs have been required for several other prescription drugs, principally oral contraceptives and estrogen products. In 1975, at the urging of consumer groups and the FDA National Advisory Committee, FDA undertook a "Patient Prescription Drug Labeling Project" to explore the possibility of more general PPI requirements for prescription drugs. Research was conducted and national symposia were held in 1976 and 1978 to examine issues raised by this idea. FDA concluded that PPI requirements should be extended to a much wider range of prescription drugs, but it also decided that careful evaluation studies should be done concurrently as a guide to future policy development.

The Institute of Medicine was asked by FDA to recommend a research agenda for the evaluation of the effects of PPIs. An Institute study committee examined the existing literature, held a public hearing to receive the views of interested parties, and discussed research needs and evaluation approaches at several meetings before reaching the conclusions stated in this report. Because there has been such widespread interest in PPIs, the committee did not confine itself to discussing research that would be of presumptive interest to a regulatory agency. A number of valid topics for investigation (for example, the impact of PPIs on the role of the pharmacist) may be of less concern to FDA than to other organizations, groups, or persons. The committee hoped to encourage support of research by agencies or organizations that might have an interest in the effects of PPIs on particular types of patients (such as children, the elderly, or cancer patients), on the development of professional roles (of the pharmacist or the nurse, for example) or particular types of health care settings (such as HMOs), or for cost-reducing purposes (such as changing the extent of use of generic drugs or drugs of doubtful efficacy).

This report addresses priorities and methods for evaluating the effects of PPIs, not policy questions about the development and distribution of PPIs. The report deals primarily with evaluating PPIs as they are used rather than with such topics as basic research on the processes by which written information is comprehended or recalled. In reaching its conclusions, the committee gave particular attention to

(a) the variety of possible effects of PPIs that have been predicted by persons advocating and opposing FDA's plans for PPIs, (b) the research literature on the effects of PPIs and other forms of written materials used to promote the safe and effective use of medications, and (c) research approaches for the assessment of the possible effects of PPIs.

Research Evidence

A growing body of research contributed to the committee's understanding of the possible effects of PPIs and its assessment of needs and priorities for future research. Only limited data now exist on the effects of actual PPIs, although several surveys show that patients are interested in obtaining written information about the proper use and possible hazards of the prescription drugs they use. From the studies reviewed in the report (Chapter 2), the following general conclusions can be drawn:

-- Patients' evaluations of the PPIs have been quite positive. Evidence is lacking, however, on the extent to which patients will continue to make use of PPIs as they become more routine.

-- A substantial literature exists on the topic of patient compliance with therapeutic regimens, and in many of these studies written information about drugs is used. The results of such studies have been mixed. Success in improving compliance with drug therapy for acute illness has been reported in some instances (for example, antibiotics against infection). But the effect of written information on compliance with long-term therapeutic regimens (for example, antihypertensive drugs) is generally minimal. It is difficult, however, to evaluate much of this literature in terms of the likely effects of PPIs because the written drug information differs in tone, content, and intent from PPIs. Furthermore, many of the studies do not distinguish the separate effects of the written information from the effects of the larger health education programs of which it is a part. The usefulness of this literature for predicting the effects of PPIs as they are actually used in medical practice is limited.

-- Some results are beginning to be reported from well-designed experimental studies of the effects of PPIs on patients, and two important studies are underway. The data now available indicate that patients tend to read PPIs and find them useful, and that some increase in patients' knowledge may result. Although available evidence is sparse and inconclusive, studies to date have not found that PPIs increase the incidence of side effects or the demands of patients on health practitioners.

-- Almost no research has been reported on the ways that PPIs are actually distributed and used in settings that are not under some degree of control by researchers.

-- Almost all research on the effect of PPIs has been concerned with their effects on patients. The effects on practitioners'

communication habits, on the role of the pharmacist or the nurse, and on prescribing patterns are largely uninvestigated. Almost no data are available on the costs associated with the development and use of PPIs.

-- No information is available on any long-term changes that may be associated with the use of PPIs. Nor is information available on the extent to which short-term changes may prove stable over time.

Purpose and Predicted Effects of PPIs

The evaluation of PPIs could focus on their cost and whether they accomplish their purpose. The committee believes that evaluation efforts couched in such narrow terms would be inadequate, because much uncertainty and disagreement exist about the purpose of PPIs, and some of the most important effects of PPIs may be unintended or incidental to their primary purpose. Both of these considerations are important to the overall strategy for the evaluation of PPIs.

First, various concepts exist about the purpose of PPIs. Some persons concerned with health policy view them as having only the purpose of providing patients with information to which they are entitled. An evaluation of PPIs from this standpoint might be concerned only with such basic matters as whether PPIs are read and appreciated by patients. Other persons, however, see PPIs as serving a variety of functions, such as increasing patients' knowledge, improving the safety and efficacy of drug use, stimulating better communication between practitioners and patients about the use of drugs, and improving physician prescribing practices. In short there is no agreement on a single goal against which PPI effects can be measured. The purpose of PPIs may vary to some extent even from drug to drug: the primary purpose of the isoproterenol inhalator PPI was to warn patients against improper usage, but the primary purpose of the oral contraceptive PPIs was to assist patients in making informed decisions about using that method of birth control. The evaluation of PPIs must be in terms of purposes, rather than a single purpose.

Second, there is great concern about, and interest in, the possible incidental or unintended effects (both positive and negative) that PPIs may produce. A wide variety of effects have been predicted, many of which have sufficient plausibility to merit their being assessed in evaluation studies.

The various effects that have been predicted for PPIs can be summarized in outline form. Some of these effects pertain to the purpose of PPIs; others pertain to effects that may be incidental or unintended. All may be suitable objects for empirical study. The predicted effects of PPIs fall into a relatively small number of categories:

1. Patients' cognitive and attitudinal responses
2. Patients' behavioral responses

a. Decisions regarding whether to use drug
   (1) Initially
   (2) Under various other circumstances (for example, with other drugs, in combination with certain foods and drink, or when engaging in such activities as driving or vigorous exercise)

b. Usage of drug as intended by the physician
   (1) proper dosage and course of therapy
   (2) proper precautions and monitoring of side effects
   (3) self medication

3. Incidence or perception (and attribution to the drug) of side-effects or adverse reactions
4. Therapeutic outcomes
5. Doctor-patient relationship and communication
6. Physician's attitudinal responses
7. Physician's prescribing and referral behavior
8. Pharmacist's role (duties, relationships, and attitudes)
9. Nurse's role (duties, relationships, and attitudes)
10. Cost
11. Liability
12. Broad "systems effects" in the organization and delivery of health care.

Many predictions of effects of PPIs are mutually contradictory. For instance, it has been predicted both that PPIs will improve the effective use of drugs by providing patients with clear instructions, and that PPIs will frighten or confuse patients to an extent that they will not use medications for which there are sound indications. It has been predicted both that PPIs will reduce the incidence of adverse reactions by informing patients of necessary precautions and possible interactions (for example, between the drug and alcohol), and that PPIs will increase the incidence or perceptions of side effects by telling patients that they may occur. It has been predicted both that PPIs will prompt physicians to have more extensive discussions with patients about drugs being prescribed, if only to prevent later anxious questioning over the telephone, and that PPIs will come to substitute for doctor-patient communication.

Contrary predictions may each prove to have some validity, because the effects of PPIs may vary according to the characteristics of the drug, the types of patients using the drug, the settings in which the drug is prescribed and used, the content and tone of the PPI, and so forth. In the committee's view, the planning of research will not be guided adequately by the expectation of learning which of a pair of conflicting predictions is correct. Instead, the goal should be to identify the circumstances under which predicted effects do or do not occur. Thus, care must be taken to examine the use of PPIs in a variety of settings and with different types of drugs and patients. Almost all effects that have been predicted for PPIs may occur with some patients and some drugs under some circumstances, although the research to date suggests that many of the hopes and fears about PPIs may prove to be exaggerated.

Research Needs

The committee identified several considerations that should be reflected in research strategies for evaluation of PPIs. First, research should be designed that will assess planned and unplanned, and positive and negative effects of PPIs. Second, research plans should take into account that the overall impact of PPIs may involve both direct effects, resulting from the exposure of patients to specific PPIs, and more general effects resulting from the fact that PPIs are in use. The former include questions whether PPIs affect patients' knowledge or behavior; the latter are suggested by hypotheses that PPIs will produce changes, for example, in physicians' communication patterns with patients, the role of the pharmacist, or prescribing practices.

Third, it should be recognized that the effects of PPIs are likely to vary according to characteristics of drugs, patients, physicians, and health care settings. Therefore, care should be taken in generalizing the results of any particular study, and attempts should be made in future studies to maximize variation in the types of patients, drugs, and health care settings studied. Fourth, the importance of the time dimension must be recognized. Some effects may occur as an immediate response to PPIs, while others may take a relatively long time to develop. Some short run effects may not be stable over time. Finally, priorities for new research should be influenced by recognition of the research that has already been conducted. If studies presently underway are included, direct effects of PPIs on patients' knowledge, attitudes, and behavior have been the object of much more research than the effects of PPIs on, for example, physician behavior. Similarly, more research has focused on patients' responses to PPIs under controlled conditions than on the ways that PPIs will be distributed and used in a variety of real-world settings.

Many questions and issues have been raised that would link PPIs to a wide variety of possible outcomes. The committee found that the study of most of these outcomes could be comprehended within three general research approaches. First are questions about the ways that PPIs will be distributed and used. Such questions deserve highest priority at present and are best studied through the use of descriptive social research methods. Second are questions about patients' responses to PPIs. Such questions are best studied through the use of well-designed experiments. Third are issues involving the long-term consequences of the use of PPIs. A wide variety of longitudinal research approaches will be needed to assess these questions, and some will deserve high priority attention in the future. These three general types of studies are described in more detail below.

The Use of PPIs

In evaluating the expanded requirements for PPIs, information will be needed regarding the ways they come to be distributed and used. Studies should be undertaken simultaneously with the introduction of PPIs to examine such basic matters as whether and how patients receive PPIs;

in what manner they are used (for example, read and retained for future reference); patients' assessments of the usefulness of PPIs and the information contained therein; physicians' awareness of, experiences with, and attitudes toward, PPIs; the extent to which the PPI stimulates communication between practitioners (physicians, nurses, or pharmacists) and patients or their families, or causes qualitative changes in practitioner-patient relationships and decision-making therein; and physicians' use of the option of instructing that PPIs not be given to patients, if that option is available under the regulations. To date, very little descriptive research has been reported on the use of PPIs, because so few PPIs have been in use.

The committee concluded that descriptive research methods from the social sciences are the most appropriate approach to this set of questions. The use of experimental design to study many of these questions is not feasible, and the essential need is for information about PPIs used in natural, rather than controlled, settings. The literature on such topics as doctor-patient communications, pharmacy practice, physician attitudes, and patient satisfaction provides a variety of useful methods including direct observation, video and audio-taping, the use of questionnaires and interview schedules, and the use of existing records and data on such matters as prescribing patterns.

The use of PPIs involves medical practice, pharmacy practice, and patients; an impact on one element (for example, on the patient) may produce secondary effects on other elements. For these reasons, descriptive studies should include and link the three elements. The committee suggests that FDA support studies in several (4 to 6) communities or neighborhoods, so that an examination can be made of the use of PPIs by persons of various ages and backgrounds and in different types of medical and pharmacy practice settings. In any of these studies, the committee calls attention to the necessity that FDA's direction or sponsorship be insulated from its enforcement activities and that care be taken to assure the confidentiality of data obtained in the research. On a smaller scale, solo investigators could conduct sharply-focused descriptive studies of aspects of the distribution and use of PPIs, or their use by a particular patient population or under particular circumstances.

Research also is needed to obtain baseline information, preferably in the communities to be studied after the introduction of PPIs, on the persons and the settings that will be affected by their use. The committee also suggests that the feasibility be examined of conducting some parallel research in Canada, where there are no plans to introduce PPIs, to examine practitioner and patient attitudes as compared with those in the United States, both before and several years after the initiation of PPIs here. Information from before-and-after comparisons would bolster assessments of the effects of PPIs on such matters as practitioner-patient communication, patients' attitudes about what information they should receive and how much they should participate in decisions affecting their own health care, patients' satisfaction with the health care they receive, and the like.

Effects of PPIs on Patients

Experimental studies in which patients are randomly assigned to receive PPIs or "placebo" drug information of a more general nature constitute the soundest way to test the many hypotheses that have been offered regarding PPI effects on the knowledge, behavior, and attitudes of patients. Do PPIs increase patients' knowledge? Do PPIs confuse patients? Do PPIs affect patients' optimism or pessimism about their condition and the likelihood that the medication will be of benefit? Do PPIs help patients use medications properly? Do PPIs affect therapeutic outcomes or the experience, attribution, and reporting of side effects? Do PPIs alter patients' attitudes of trust and confidence in the physician? Are patients who receive PPIs more or less likely to share medications with others? Such questions are best answered through the well-designed experiments; other methods will lead to questionable or even erroneous conclusions.

These aspects of patients' responses are of central importance to the evaluation of PPIs and are the subject of a growing body of research. Sound experimental research designs have been or are being used in the study of patient responses to PPIs for thiazides (diuretics used chronically in hypertension), estrogens, an antibiotic (erythromycin), a hypnotic (flurazepam), and a minor tranquilizer (diazepam). These studies will provide information about outpatient responses to PPIs on many relevant issues, such as compliance, patients' decision-making, incidence of side effects, and patient confusion and anxiety.

Because this body of research is expanding, the committee regards additional experimental research on PPI effects on patients as of lower priority than the descriptive research described earlier. However, in light of the widespread concern about possible negative effects of PPIs on patients, some additional experimental research seems warranted. The committee had extensive discussions about variations among drugs and among types of patients and conditions for which drugs are used, and concluded that it is reasonable to expect such variations to be associated with differences in the effects of PPIs on patients. It is desirable, therefore, that dimensions such as the following be comprehended in studies using an experimental design:

- Drugs used for acute conditions and drugs used chronically, since compliance studies show that patients' responses to the one type may not be generalizable to the other.

- Drugs that typically produce no effects of which patients are aware, and drugs that produce subjective effects, because of possible variation in the role that the PPI may play in patients' interpretations of their responses to the drug.

- Drugs with relatively high and low risk, since a major concern regarding PPIs is whether patients will be able to understand and properly interpret discussions of risks and side effects in PPIs.

- Drugs for which there are recognized compliance problems, since improved compliance is frequently cited as a benefit of PPIs.

- Drugs for which mistakes in use may have serious implications, since a reduction in errors is another hypothetical benefit of PPIs.

- Drugs to which patients may seek access access from physicians to meet self-defined needs (for example, weight loss or assistance in sleeping), since it has been suggested that PPIs may curb patients' demands for drugs.

Many of these dimensions have been covered in past experimental studies of PPIs or studies now under way. The selection of drugs for future studies should maximize the number of additional dimensions that are studied. In addition, a greater variety of types of patients and health care settings should be included. In the committee's view, some existing experimental studies, which have used both randomization and "placebo" written materials (general information about drugs, but not specific to the drug being prescribed), provide a sound methodology for new research on the effects of PPIs on patients.

Trends in the Effects of PPIs

Longitudinal studies are needed to assess the broader impact of PPIs and the stability of initial responses to them. Possible topics and research approaches include the effect of PPIs on physicians' prescribing behavior, particularly with drugs that are seen as over-prescribed, drugs that are of doubtful efficacy, and drugs that are used for purposes not approved by FDA. Data from the National Prescription Audit and the National Disease and Therapeutic Index should be used to study changes in prescribing behavior that may be associated with the introduction of PPIs. Comparable studies in Canada would strengthen any conclusions about the possible impact of PPIs on prescribing trends in the U.S.

The committee also suggests that some descriptive studies be replicated several years after PPIs have come into general use. Only through such replication will trends become apparent in such matters as how patients read and use PPIs; patients' attitude toward their physicians, medical decision-making, and the use of drugs; physicians' communication behavior and perceptions of patients' expectations; physicians' modes of adaptation to PPIs, including their referral and delegation behavior; and pharmacists' adaptations to PPIs and their patterns of communication with patients.

Some changes that may be produced by PPIs are not amenable to the observational and survey approaches, experimental studies, or records studies that have been described. These topics include (1) the impact of PPIs on the liability of manufacturers and practitioners; (2) the extent to which PPIs, by possibly encouraging more extensive counseling activities among pharmacists and nurses, may generate political struggles regarding state

licensure laws, and policy disputes about third party reimbursement; and (3) the impact of PPIs on the retail pharmaceutical industry, including the development of unit-of-use packaging and the stimulation of bifurcations in the evolution of the pharmacists' role in different types of practice settings (for example, independent pharmacies vs. chain pharmacies). Assessment of these effects by scholars in the appropriate disciplines (for example, law, medical sociology, political science, or the sociology of occupations) should be encouraged.

Because of the great concern about health care costs, FDA should particularly be prepared to assess the new costs and cost savings associated with PPIs. This can be done in part by examining the cost-relevant aspects of the studies recommended earlier. For example, there are important cost implications in questions whether PPIs will increase or decrease the counseling activities of physicians and pharmacists, whether they will alter patients' demand for drugs and the prescribing practices of physicians, and whether they will affect the incidence of adverse reactions. In addition, independent estimates can be prepared to portray the costs associated with the development and distribution of PPIs.

Finally, in instances where experimental studies of patients' responses to PPIs have played an important role in policy decisions regarding PPIs, key work should be replicated three to five years after PPIs have come into general commerce to determine the extent to which any major beneficial or harmful effects of PPIs are enduring.

Conclusion

This report suggests studies that should be undertaken in response to FDA's planned regulatory actions to require the more general use of patient package inserts with prescription drugs. Most of this research is on the distribution and use of PPIs and on their effects on attitudes, behavior, and relationships of patients and health professionals. Although the immediate purpose of this research is to contribute to future policy decisions regarding PPIs, it may also contribute more generally to our knowledge of therapeutic relationships, processes of change in the health care system, and the behavior of patients, physicians, and other health professionals. Useful knowledge may be gained about different ways of organizing or paying for health care; the role and effects of PPIs may vary according to such factors as the ready availability of consultation, the presence of ancillary personnel, and the modes of reimbursement. Finally, research on PPIs may increase our understanding of the processes by which governmental regulatory actions have effects beyond their original purposes.

CHAPTER 1

THE PRESENT POLICY CONTEXT

The U.S. Food and Drug Administration (FDA) is developing regulations* that would mandate that patients be provided with written information, in the form of patient package inserts (PPIs), about the purpose, risks, and proper usage of various prescription drugs. This idea has provoked both positive and negative reactions, and predictions of a variety of beneficial or harmful effects on patients, health care providers, and the health care system in general. Some research to assess the possible effects of PPIs has been conducted or is underway at the present time, and more is contemplated as PPIs come into wider use. The FDA requested that the Institute of Medicine review the state of knowledge about the possible effects of PPIs and make recommendations to assist in the further development of research to assess these effects.

Historical Background

Although the idea that the government should require that detailed written information generally be provided to patients receiving prescription drugs is relatively new, governmental regulation of the labeling of drugs goes back more than half a century. The Pure Food and Drugs Act of 1906 with its limiting amendments of 1912 was the initial effort by the government to regulate drug labeling by prohibiting manufacturers from making fraudulant claims of efficacy or including deceptive statements on

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the labels of drug products. FDA's early regulatory actions were against such products as a headache mixture called Cuforhedake Brane-Fude, "male-weakness" remedies such as Sporty Days Invigorator, and Dr. Johnson's Mild Combination Treatment for Cancer (Young, 1970).

The Food, Drug, and Cosmetic Act of 1938 substantially expanded federal labeling requirements for drugs. The Act required that drug labels contain directions for use, including information about indications, contraindications, dosage, instructions, and other information. However, the Act gave FDA the power to exempt drugs from this requirement "if not necessary for the protection of public health" (Cavers, 1970). The regulations issued by FDA pursuant to the Act exempted prescription drugs, as dispensed, from the labeling requirement on the condition that manufacturers would provide detailed information to physicians. In 1952 this regulation was codified by Congress in what is now section 503(b) of the present Act. Communicating important information about the drug to the patient was viewed as the practitioner's responsibility, not the drug manufacturer's. This view was consistent with the concept of the prescription drug, which was defined in part by its being unsafe unless administered under the supervision of a licensed practitioner. Within this conceptual framework, not only would a patient package insert be unnecessary, it could even be counterproductive because it could encourage self-medication by patients with drugs for which medical supervision was, by definition, necessary for safe use (Merrill, 1973). Thus, the seeming paradox developed by which specific labeling information was provided to patients with over-the-counter medications, such as aspirin, but with drugs that were potentially more hazardous and were therefore available only by prescription, the labeling for patients has generally included only such basic information as the name of the drug, usage instructions (for example, take four times a day), and the name of the pharmacy and the prescribing physician. Such an approach was consistent with prevailing ideas about the proper role of the patient and functions of the practitioner.

These ideas, which have changed rapidly in recent years, held sway at FDA for some time even after the agency first required patient labeling for a prescription drug in the late 1960s. That and later requirements were seen as exceptions, not as implying a general need for patients to be provided with such materials. As recently as 1973, a knowledgeable observer of the Food and Drug Administration could comment that FDA's "long-standing suspicion of self-medication suggests that it (FDA) is not likely to become a strong proponent of providing consumers more information about individual prescription drugs" (Merrill, 1973). FDA's view changed rapidly, however, and the PPI concept gained the support of top FDA officials (see, for example, Schmidt, 1977). By the mid-1970s, preliminary work on a general PPI requirement was underway at FDA.

Development of PPI Requirements

In 1968, FDA first required drug labeling information for patients receiving a prescription drug. Evidence had developed that isoproterenol inhalators, if used excessively by bronchial asthma patients, could

produce an effect (bronchoconstriction) opposite to the intended effect. FDA determined that users of the inhalator should be warned about this hazard, and manufacturers were required to include patient package inserts with the inhalator. In the period since that first PPI requirement, concepts of the patient's right to information have gained increasing legal and political force, and doubts have grown about the advisability of relying solely on spoken communication to transmit important information to patients about the use and effects of prescription drugs. The use of PPIs has slowly expanded; since 1970 FDA has issued PPI requirements for oral contraceptives, intrauterine contraceptives, diethylstilbestrol (DES) if marketed as a postcoital contraceptive, and most recently for progestational drug products.

Contraceptive drugs and devices, used by a well population for long periods of time and for which alternative contraceptive methods exist, raise significant benefit-risk considerations. FDA determined that the traditional methods of communication between physician and patient for conveying information on potentially hazardous effects should be supplemented. To encourage women to assess the benefits and risks associated with the use of these agents, FDA required PPIs to provide information on effectiveness (in comparison with other contraceptive methods), contraindications, warnings, precautions, and adverse reactions. Increased patient participation in the decision to use such drugs is clearly an intended outcome for these inserts.

The estrogen PPI was required for similar reasons, but it appears that FDA also hoped that this requirement would serve an additional function--reducing the extent to which these drugs were prescribed. "In the case of estrogens," Commissioner Kennedy has stated, "prescribing had clearly gotten out of hand...the majority of estrogen prescriptions were being written for elective post-menopausal indications for which there is no evidence of efficacy, but a substantial known risk elevation for endometrial cancer" (Kennedy, 1978). The agency apparently believed that if information about such risks was made available to patients, questionable uses of the drug would decrease.

This brief description of existing regulations to require prescription drug labeling for patients suggests that PPI requirements have evolved in response to several different needs and concerns. Ensuring the safe and effective use of drugs has been a general underlying goal of PPI requirements, but there also appear to be other motivations, as with estrogens. Doubts and disagreements exist about the purpose of PPIs and FDA's reasons for proposing them. Some see the PPI as a straightforward method for providing patients with information. Others see it as a back-door method for increasing governmental control over the practice of medicine. Whatever the purpose of the PPI, many commentators see in it the potential for widespread effects in medical care. This report concerns ways in which those effects can be assessed.

Pressures for Change

The consumer movement, which has played a significant role in fostering a wide variety of governmental and non-governmental programs and activities to educate consumers and to involve them in decision-making, is clearly involved in the recent history of PPIs and in the attempt to make them a general requirement with prescription drugs. The most concrete manifestation of this effort was a petition filed with FDA in 1975 on behalf of a number of consumer organizations requesting that the agency require patient-directed labeling for prescription drugs, particularly drugs that present dangers to pregnant or breast-feeding women and drugs that are widely used and overprescribed. The petitioners made a number of arguments in support of such a requirement, including concern that physicians may not always provide patients with the information needed to use drugs safely and effectively, that patients may not understand the information provided orally and may be reluctant to ask questions, and that patients may need written material in case they forget the information that was provided orally (Center for Law and Social Policy, 1975).

In response to interest by consumers and to the suggestions of the agency's National Food and Drug Advisory Committee, the FDA inaugurated a Patient Prescription Drug Labeling Project in 1975 to consider the feasibility of requiring PPIs for a wide variety of prescription drugs (Morris, 1977). FDA solicited opinions and thoughts about implementing a PPI program from representatives of consumer groups, medical associations, the pharmaceutical industry, pharmacy and allied health organizations, and others. In 1976, and again in 1978, FDA sponsored national symposia to collect views on PPIs from numerous interested groups and to explore a variety of issues (what should PPIs contain? how should they be prepared and distributed? what exceptions to a general PPI requirement are warranted?) raised by the proposal that PPIs be generally required for prescription drugs. Another aspect of FDA's Drug Labeling Project has been the conduct and support of research to evaluate existing PPIs (particularly for oral contraceptives) and alternative prototypes of possible future PPIs. (This study by the Institute of Medicine is intended to assist in the further development of a research program to assess the effects of PPIs.)

The increased interest in PPIs also has been reflected by Congress, which has recently considered legislation that, among other matters, would broaden the applicability of the PPI requirement. Proposed legislation, called The Drug Regulation Reform Act of 1978 (S.2755 and H.R.11611), would have required prescription drug labeling for patients, which contained information about the purposes for which the drug is intended, precautions, potential significant side effects and adverse reactions, warnings against unsafe use, storage instructions, and "any other information that the Secretary finds necessary to protect the public health or to promote the safe and effective use of the drug product by patients" (S.2755). The bill also included a provision to allow the practitioner to direct that labeling information be withheld from a patient unless the Secretary has determined that the nature, use, or method of administration of the drug product required an informed decision by a patient regarding whether to use the drug.

Although the bill never came to a vote in the last Congress, the labeling requirements for patients remained basically intact through committee markup sessions, and similar provisions are included in bills introduced in the 96th Congress.

Justifications for Expanded PPI Requirements

Two principal lines of argument have been offered in support of the PPI concept, a situation that complicates the task of focusing PPI evaluation efforts. The first argument pertains to making drug use safer and more effective. The second pertains to patients' rights to have information that is relevant to decisions about their medical care. While in many cases these two arguments reinforce each other, some commentators see them as conflicting, at least with regard to some drugs.

Safe and Effective Drug Use

The first argument in favor of PPIs is that the wider availability of information about the risks and proper use of drugs will produce a general increase in knowledge about drugs and their safe and efficacious use. Such benefits are seen as resulting not only from the direct effects of PPIs on patients' knowledge and behavior, but also from the effects of the PPIs on practitioners, who may themselves learn from the PPI in anticipation of, or in response to, questions raised by patients. Among the topics frequently raised in such arguments in favor of PPIs are the high volume of drugs prescribed in the U.S., the problem of adverse drug reactions and drug-drug interactions, the misuse of some drugs by patients and by physicians, and inadequacies in the physician-patient communication process.

Volume of Drugs One element of concern is the volume of drugs used in the U.S. The number of new and refill prescriptions dispensed has increased four-fold since 1950—to 1.4 billion in 1977 (Silverman and Lee, 1974; National Prescription Audit, 1977). More than 42 percent of all office visits to physicians in 1976 resulted in a drug being prescribed (U.S. DHEW, 1978), and hospitalized patients average one prescription for each day of hospitalization or about eight for a typical hospital stay (Silverman and Lydecker, 1977). Many factors contribute to the increased use of drugs, such as the discovery of new and more effective agents, the increase in the elderly population, wider health insurance coverage, and improved access to health care services. But the magnitude of drug prescribing and consumption has heightened concerns about a too-ready reliance on medication, the misuse or abuse of some drugs, the occurrence of adverse reactions, and questionable prescribing practices.

Adverse Drug Reactions Some arguments in favor of PPIs stem from concern about adverse drug reactions, which have been reported to contribute substantially to morbidity, to health care costs, and even to mortality. Studies have indicated that adverse drug reactions may be responsible for between 1.7 percent and 4.5 percent of hospital admissions,

may cost from $1 billion to $3.5 billion annually, and may result in as many as 140,000 deaths annually (Caranasos et al., 1974; Silverman and Lee, 1974; Talley and Laventurier, 1974; Lee, 1978). The methods by which such estimates have been derived have come under serious criticism (Karch and Lasagna, 1974), but there is widespread agreement that the problem of adverse drug reactions is significant.

The potential role of the PPI is difficult to assess, because almost no studies address the question of what drug reactions are preventable, as distinct from those that are unavoidable or unpredictable because of an inherent drug toxicity or "idiosyncratic" response (Karch and Lasagna, 1974). Numerous variables make it difficult to assess accurately the cause-effect relationship between the drug and the reaction. Nevertheless, a number of factors believed to contribute to the occurrence of adverse drug reactions suggest many reactions may be preventable. These include the overprescribing or inappropriate prescribing of some drugs, the lack of clear therapeutic objectives in some prescribing, "polypharmacy" or the prescribing of multiple drugs, inadequate patient and physician knowledge about drugs, and deficits in the present state of biomedical knowledge about the physiologic variables that may interact with generally safe drugs to produce adverse reactions in some patients (Melmon, 1971).

Prescribing Practices Interest in how drugs are being prescribed is particularly strong concerning antibiotics, psychotropic agents, hormones, and analgesics (Lee, 1978; Silverman and Lee, 1974). Inappropriate and unjustified prescribing of antibiotics, for example, has been documented repeatedly in inpatient and outpatient settings. One study of patients in a university hospital concluded that 64 percent of all antibiotic therapy either was not indicated or involved an inappropriate drug or incorrect dosage (Castle et al., 1972). Other studies show similar prescribing practices in hospitals, including widespread use in patients with no evidence of infection (Scheckler and Bennett, 1970; Roberts and Visconti, 1972). A review of studies on prophylaxis with systemic antibiotics in surgery revealed that such therapy is often unwarranted—being used for longer periods that can be justified and used after some types of surgery where it serves no value in reducing wound infections (Chodak and Plaut, 1977).

Antibiotics are misused in office practice as well (Stolley and Lasagna, 1969; Stolley et al., 1972). Studies of drug prescribing in community practice indicate that antibiotics are the most commonly dispensed drugs, often being prescribed for such trivial complaints as the "uncomplicated common cold" (Stolley et al., 1972; Simmons and Stolley, 1974; Lee, 1978). Although data that identify both the prescription and the reason for prescribing an antibiotic are limited, such questionable practices as prescribing an antibiotic without having taken a culture, prescribing an antibiotic (by phone) without examining the patient, and prescribing an antibiotic for a viral illness apparently occur with some frequency (Simmons and Stolley, 1974). In both hospital and community practice, it appears that antibiotics are indiscriminately prescribed

for "prophylactic" purposes—a practice that has been criticized because of the lack of evidence of efficacy for many such uses and because of the hazards implicit in such practices, especially the emergence of antibiotic-resistant bacterial strains that are increasingly difficult to control (Simmons and Stolley, 1974; Lee, 1978).

Although there is some difference of opinion about what constitutes appropriate uses of psychoactive drugs, there is nevertheless evidence that this class of drugs is overprescribed (Lee, 1978; Institute of Medicine, 1979). Among the most freqently prescribed psychoactive drugs are the minor tranquilizers, especially diazepam (Valium(R)) and chlordiazepoxide (Librium(R)). Although evidence indicates that minor tranquilizers are efficacious, at least in the short run, in treating patients with anxiety or insomnia, only a minority of prescriptions for minor tranquilizers are for these problems. As much as 70 percent are for a variety of complaints, including hypertension, angina, peptic ulcer, and asthma, for which there is no evidence of efficacy (Lee, 1978; Waldron, 1977). Decisions to prescribe some psychotropic drugs may not be based strictly on medical need. Some factors believed to contribute to overprescribing include the increasing tendency to define social problems as medical problems, extensive advertising and promotion of these drugs by pharmaceutical manufacturers, the structure of medical practice and its time constraints, and pressure from the patient for a prescription (Waldron, 1977; Muller, 1972). In addition to creating a potential for occurrence of adverse drug reactions and interactions, overprescribing of psychoactive drugs may have more insidious effects, such as a tendency to depend more and more on medical interventions, especially drug therapy, to solve problems that are not primarily medical, and a reluctance to pursue alternatives.

The greater public availability of information about drugs, whether through PPIs or other means, may increase the knowledgeability about proper uses of drugs, which could help reduce questionable prescribing practices. The link between inappropriate drug use and patient information was made, for example, by the study committee in the recent Institute of Medicine report, Sleeping Pills, Insomnia, and Medical Practice. As a response to the evidence of inappropriate use of these medications, one recommendation made by the IOM committee was that patients should be provided with "clear directions and warnings about the use of hypnotic drugs" (Institute of of Medicine, 1979).

Misuse by Patients Another problem with drugs is that patients frequently do not use them properly. A recent review of 185 studies of compliance* with a variety of medical regimens indicated that for patients

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* The committee recognizes that the "compliance" concept has some undesirable implications about the role of the patient and the responsibilities of the physician. However, because the term has come to be used to characterize an important and well-known problem (even if the term may imply too much regarding the cause of the problem), and alternate terms are unwieldy, the committee has continued to use the word compliance.

with acute illness, rates for properly following drug regimens ranged from 18 percent to 89 percent (Sackett, 1976). In long-term therapy, the average compliance among different illnesses was 54 percent; about one-third of the patients took none of their medications, one-third of the patients took almost all, and the remainder were within this range. A second literature review of studies pertaining specifically to compliance with prescription drug therapy concluded that fewer than six out of ten patients take their medications as intended by prescribers (Mikeal and Sharpe, 1974). Other researchers have estimated that between 25 percent and 59 percent of patients will make errors in taking prescription drugs, and for between 4 percent and 35 percent of these patients this misuse could pose a serious threat to their health (Stewart and Cluff, 1972). Although the explanation of some types of compliance problems involves complex questions of motivation and behavior change—as with long-term therapy to reduce hypertension--other problems of compliance may result from patients' lack of information about, or understanding of, the proper use of drugs. It is with such problems that PPIs are expected to play a useful role.

Doctor-Patient Communication Early studies of compliance, as the term itself suggests, viewed the patient as the source of the problem. Although a number of determinants of compliance have been documented, and the problem should not be oversimplified, it is apparent that the physician-patient communications process plays a role. Inadequate communication between physician and patient, such as failure to convey to the patient information about the purposes of the drug, expected outcomes, length of drug regimen, and dosage schedule, have been found to contribute to non-compliance (Hulka et al., 1976; Svarstad, 1976; Francis et al., 1969). Increased information exchange between doctors and patients has been found to correlate with decreases in drug error rates and greater conformity with the drug regimen (Korsch and Negrete, 1972; Svarstad, 1976; Hulka et al., 1976).

Even when information is provided to patients, however, there are a number of factors that determine whether it will be understood and remembered. Anxiety about the medical encounter may result in the patient not paying attention to the instructions of the physician. Instructions that are technical, jargon-laden, or ambiguous may be difficult for the patient to interpret properly and may result in medication errors (Powell et al., 1973; Hermann, 1973; Mazzullo et al., 1974). Patients' reluctance to ask questions of the physician further contributes to this lack of understanding by the patient about proper drug use (Shuy, 1976). For all of these reasons, a useful role has been seen for written information and instructions.

To summarize, the first major argument in favor of PPIs concerns increasing the safety and efficacy of drug use. This argument refers to the amount of drugs now being prescribed (and recognizes that any pharmacologically-active substance carries some degree of risk), the existence

of some poor prescribing practices by physicians and misuse of drugs by patients, the problem of adverse drug reactions, the "compliance problem," and the existence of various flaws in doctor-patient communication. Although no one expects that the PPI is a complete solution for these problems, it is thought PPIs will make a contribution by giving patients clear instructions, by prompting them to ask questions, and by raising their general awareness about the proper use of drugs and the dangers of misuse.

Critics of the line of argument described in this section have generally expressed skepticism that PPIs will produce benefits regarding such matters as the overuse or misuse of drugs, the incidence of adverse reactions, or problems with compliance. They have also offered a contrasting vision about possible effects of PPIs. They assert that PPIs will produce unwanted side effects through suggestion, frighten patients and make them reluctant to take needed medications, and foster confusion and disruption in doctor-patient relations. Such disagreements and contradictory predictions have contributed to the recognition for the need for research to evaluate the effects of PPIs. The extent of our current knowledge regarding the positive and negative effects of PPIs is summarized in Chapter 2.

Right-to-know Arguments

The second major argument for PPIs concerns patients' rights to have information that will enable them to assume greater involvement in decisions regarding their medical care. This idea is rooted in societal values regarding egalitarianism and individual autonomy. While such involvement by patients may lead to more safe and effective use of at least some drugs (little empirical research is available on the point), the right-to-know argument for PPIs is quite distinct from the argument regarding safe and effective drug use.

While this is essentially an argument based upon values, it does have an empirical dimension. Evidence from several sources indicates that patients want information that would allow them a greater role in decisions about whether to use certain drugs or to make them more informed users of these drugs. In an FDA-sponsored survey of a national sample of 1,321 consumers, about one-half indicated a desire for more information about prescription drugs and most of the these respondents preferred written information (Knapp, 1974). In another survey of inpatient and outpatient populations, patients indicated that they felt that physicians should provide drug information with each prescription, even if not directly requested by the patient; they also indicated a preference for both detailed PPIs and a summary (Joubert and Lasagna, 1975). Both surveys suggest that the most interest in such material is found in the younger and better educated segment of the adult population.

Several consumer surveys and demonstration projects have shown written communications to be an important source of information for specific prescription drugs and that study patients wanted patient-oriented

information to be included with more drugs (Wiebert, 1977; Noyes and Gordon, 1975; Ryan and McMahon, 1977; Morris et al., 1977; Kanouse and Morris, unpublished). In a recent survey of oral contraceptive users and former users, more than two-thirds of the current users preferred detailed booklets to the shorter PPI with all drugs; about one-fifth favored the PPI; and seven percent responded that both types of information should be provided with all prescription drugs (Morris et al., 1977; Applied Management Sciences, 1975). Another indication of consumer interest in information about prescription drugs is the publication in recent years of a number of lay-oriented books and pamphlets in which information about drugs is presented in considerable detail (for example, Burack, 1977; Graedon, 1977; Jones, 1977; Evans and Cole, 1978).

As has been noted earlier, several of FDA's past PPI requirements clearly have been based in an important way on the idea that patients should be given information so that they can make their own decisions. This is seen also in Commissioner Kennedy's recent statement that the most important goal for PPIs is promoting the involvement of patients in decisions regarding their care (FDA Consumer, 1978). This goal has been most clearly operable in the patient labeling requirements for elective or optional drugs such as oral contraceptives. However, definitions of what drugs are "optional" are not immutable and may vary to some degree within the population. Thus, even the use of drugs that have sound medical indications (for example, some cancer chemotherapeutic agents) may be regarded as optional from the standpoint of a particular patient. Only if patients are informed can they exercise their options. This is the basis of the "right-to-know argument" for PPIs.

Although few, if any, persons have argued that patients do not have a right to information about the drugs that they use, the right-to-know argument has nevertheless produced some objections. It is argued, for example, that the necessary information is already available to patients through physicians, pharmacists, or readily available reference materials and that right-to-know arguments do not provide any guidance regarding additional topics or details that patients need. Another argument concerns the costs that will be associated with a PPI program and questions how a value such as "right-to-know" can be weighed against that cost. One proposal made in this regard is that market mechanisms should be brought into play whereby the patient wanting a PPI would pay for it.

The right-to-know argument involves primarily philosophical, rather than empirical, issues, and it concerns policy decisions that must be made before PPI requirements are issued (such as what should be included in PPIs). Thus, neither side of the right-to-know argument is likely to be addressed extensively in a program of research to evaluate the effects of patient package inserts.

Conflicts regarding the purpose of PPIs Another area of disagreement regarding the purpose of PPIs concerns whether there is a conflict between the purpose of educating patients so as to facilitate safe and effective drug use and the purpose of promoting greater patient involve-

ment in decision-making. Serious doubts have been expressed about the feasibility of attempting to integrate the goal of encouraging patients to use prescribed drugs safely and effectively (the "patient compliance" goal) with the goal of providing the information that patients want or need in order to participate more fully in decisions about their care. In this view, the goal of improving patient compliance may be frustrated by detailed disclosures regarding risks and side effects. In the view of one commentator, these purposes are irreconcilable because the concept of patient education is designed to promote communication and cooperation while the notion of "rights" to information creates confrontation and protection (Jonsen, 1978).

On the other hand, many articles about PPIs list multiple purposes, including improved patient compliance and increased patient involvement in decision making, and offer no comments about the harmony or lack of harmony among these purposes. The authors, presumably, see no conflict among the purposes of PPIs. Other persons, however, acknowledge that PPIs can be written in such a way that, for example, the materials intended to promote the safe and effective use of the drug are emphasized to such an extent as to eclipse the PPI's usefulness for providing the balanced information that patients would need in order to make an intelligent decision regarding their use of a drug. Similarly, PPIs could include such a volume of information that any utility of the PPI in encouraging safe and effective use of drugs would be lost. Such extreme examples not withstanding, however, a balance can perhaps be struck whereby the PPI will provide information that may serve several purposes--to facilitate more patient involvement in decisions and to provide the patient with information necessary to use drugs safely and effectively. Emphases may vary to some degree from drug to drug: the use of some drugs involves a more serious and difficult decision than does the use of other drugs, and the role that patient education can serve in promoting the safe and effective use of drugs also varies to some degree from drug to drug. However, all PPIs may to some extent serve multiple purposes.

Unresolved Legal and Regulatory Issues

Although it seems clear that FDA intends to require PPIs for many prescription drugs, a number of issues still remain to be resolved including the question of FDA's legal authority to require PPIs under current law, how the PPI requirement will be implemented, and what effects are likely to result from requiring PPIs.

Although PPI requirements for oral contraceptives had been issued by FDA almost a decade earlier, the question of FDA's legal authority to require prescription drug labeling for patients was challenged in a lawsuit prompted by the PPI requirement for estrogens. The Pharmaceutical Manufacturers Association argued that Section 503(b)2 of the Federal Food, Drug, and Cosmetic Act, which exempts prescription drugs from the requirement that the patient label bear directions for use, demonstrates that

Congress did not intend that prescription drugs include labeling containing directions for patient use (Federal Register 42, 1977; Federal Register 43, 1978; Pharmaceutical Manufacturers Association v. FDA, 1977). The PMA also argued that the PPI regulation unlawfully interferes with the practice of medicine and that the regulatory action was capricious and should be set aside.

FDA has contended, however, that the primary purpose of Section 503 (b)2 was to preclude self-diagnosis and self-administration of drugs that require professional supervision for safe use, and the requirement for labeling information that would promote the safe and effective use of the drug does not contradict the purpose of the section. FDA also claims that it has authority to require labeling information for patients under the sections of the Act that provide that a drug is misbranded if the labeling is false or misleading and that failure to reveal material facts can be misleading (Sections 502[a], 502[d], and 201[m]). FDA argues that section 701(a) of the Act provides the agency with the authority to promulgate regulations for enforcing the Act, and that the Commissioner thus has the authority to promulgate PPI requirements (Federal Register 42, 1977; Federal Register 43, 1978; Pharmaceutical Manufacturers Association v. FDA, 1977).

The U.S. District Court in Delaware refused to issue a preliminary injunction against FDA's requirements for patient labeling for prescription estrogen drug products. The court found that the FDA appeared to have the edge as far as the merits of the case were concerned, that the PMA would not suffer irreparable injury in the event the preliminary injunction were denied, and that the balance of equities of other interested parties and members of the public counseled against the issuance of a preliminary injunction with respect to the estrogen PPI requirements (Pharmaceutical Manufacturers Association v. FDA, 1977). This ruling in favor of FDA's position is not the final resolution of the issue. The question of FDA's authority to issue PPI requirements remains under litigation and will ultimately be resolved in the courts or through the passage of new legislation that provides clarification.

Another legal issue of concern has been the possible impact of PPI requirements on the liability of manufacturers or health care providers. There has been much general speculation about whether PPIs will tend to increase or reduce the chances that a manufacturer or provider will be held liable in cases in which a patient is harmed through the use of a drug. Such concerns are difficult to evaluate. In no reported cases has a PPI been introduced as evidence in such a lawsuit. Further, the nature and specificity of information to be required in future PPIs, which may affect liability questions, remain unclear at this point. One attorney who has addressed this issue believes that patient package inserts may assume a legal role similar to the role played by physician package inserts in cases involving liability (Gardner, 1978). If the information in the PPI comes to mirror that in the physician insert, then the PPI may come to be used as evidence of whether a drug manufacturer has fulfilled its legal duty to warn consumers about the potential hazards of a drug--a duty currently limited to providing necessary information to prescribing physi-

cians. PPIs may also come to be used as evidence of the physician's standard of care in malpractice cases involving prescription drug injuries, or as evidence of the standard of disclosure in complaints alleging that the physician failed to obtain informed consent for drug therapy (Gardner, 1978). Depending upon the facts in particular cases, this could either increase or decrease the probability of a decision in favor of the physician. Any impact of PPIs on liability is now speculative and will be determined in court. An extensive discussion of this issue is beyond the sope of this report.

A number of other unresolved questions surround the decision by FDA to implement a PPI program. What kind of information will PPIs contain and who will prepare the PPI are questions repeatedly asked. Virtually every interested group has expressed a desire to be involved in the preparation of PPIs, and FDA (or Congress) must decide how this responsibility will be delegated. Who will distribute PPIs? Who will prepare PPIs? What provisions will be made for exceptions in the requirement to provide PPIs to patients? How will PPIs be kept current? These and many other questions will presumably be addressed in the agency's forthcoming regulations.

The Institute of Medicine Study

The major questions of interest to the study committee concern the effects that PPIs will have. (See Chapter 2 for an extensive discussion of these effects and the existing research literature.) A wide variety of predictions have been made regarding PPIs' effects on patients, health care providers, drug manufacturers, and the health care system in general.

Disagreement about whether these and other hypothetical effects are likely to occur and the fact that many of these predictions are subject to empirical assessment have led to a decision by FDA to undertake research to evaluate and analyze the effectiveness of patient labeling during the early years of its Patient Prescription Drug Labeling Project. In 1978, FDA asked the Institute of Medicine to undertake a project to recommend priorities and methods for research on PPIs. The committee was asked specifically to undertake these tasks:

- --identify potential advantages, disadvantages, costs, benefits, short and long-term effects of PPIs.
- --determine priorities for research among potential effects, types of drugs, diseases, practice settings, and patient populations.
- --determine the methods that could be used to evaluate the effects of PPIs.

Information was gathered from a review of the existing empirical literature, opinion literature, and from statements by numerous individuals and groups invited to present their views in writing or orally at a public meeting on February 13, 1979. (See Appendix A for a list of speakers presenting statements at the public meeting.) This information served as the basis for the committee's deliberations and its recommendations, which are discussed in Chapter 3.

CHAPTER 2

Effects of PPIs: Predictions and Evidence

This chapter describes the various effects of PPIs that have been predicted in testimony, opinion articles, scholarly papers, and official policy statements, and it summarizes the extent of our present knowledge about the effects of providing patients with PPIs. Although a number of studies shed light on the predicted effects and provide a sense of the plausibility of some predictions, the existing body of research does not enable us to predict with great confidence all of the possible impacts of expanded PPI requirements upon patients, health care providers, and the health care system. Some predictions have been based upon assumptions or guesses about what FDA may require regarding the contents of PPIs and their mode of development and distribution; the plausibility of such predictions is particularly difficult to assess at present. Nevertheless, the predictions and evidence summarized in this chapter provide an important basis for the committee's recommendations regarding the needs and priorities for future research to evaluate the effects of PPIs.

The existing body of research suffers from some serious limitations. Much of the evidence summarized in this chapter is based on the evaluation of health education programs in which various types of written information were used in attempts to improve patients' drug-taking behavior. Because the form, contents, emphases, and mode of delivery of these written materials may not duplicate PPIs, the applicability of their evaluation to conclusions about PPIs is not always clear. Our knowledge about the effects of actual PPIs is limited as well by the fact that drug labeling for patients has thus far been required with only a few prescription drugs involving limited patient populations. Although research based on existing PPIs--primarily studies of the effects of PPIs on oral contraceptive users--provides some very useful data, the applicability of the results to persons undergoing medical treatment, where drug therapy may be requisite to disease control or recovery, is questionable. The sex, age, and patient motivational characteristics that typify oral contraceptive users further limit the generalizability of the studies of the oral contraceptive PPI. Few data are available regarding some uses of

PPIs about which concern has been expressed, including the use of PPIs with such populations as psychiatric patients, children and adolescents, the seriously ill, and the elderly, and in institutional settings such as hospitals and long-term care facilities.

Predicted Effects on Patients

Patients' Use of, and Attitudes Toward, PPIs

Chapter 1 included evidence that, in general, consumers desire information about drugs that are prescribed for them. Such data, however, reveal relatively little about the extent to which labeling information will actually be used. A recent review of the literature on the use of labeling materials in general suggests something of the complexities involved in predicting use of labeling information (Miller, 1978). Miller found that the use of labeling materials by consumers varies according to such factors as the type of product involved, the function performed by the label—for example, Miller distinguishes among quality and performance labeling, ingredient labeling, product use and care information, and warranty labeling—and characteristics of the consumer. Regarding the latter, differences in use of labeling information are associated with such basic demographic factors as age; researchers have also distinguished between "information seekers" and "information avoiders" among consumers, with information seekers tending to be more highly educated and affluent. There are also sound reasons to expect that patients' use of labeling information will be influenced by various situational factors and by certain characteristics of the labeling, such as format, amount of detail, and tone.

Although this literature provides some basis for a degree of skepticism about the extent to which labeling information will be used by consumers, virtually all studies of patients' reactions to PPIs or PPI-like educational materials show that most patients find such written instructions to be a useful source of drug information. The studies reported to date show that PPIs, in general, have been accepted, read, and positively evaluated in terms of usefulness, although little is now known about the long-term use of labeling information with prescription drugs.

The finding that most patients react favorably to written drug information extends across a range of drugs and patient populations. In studies of patients with chronic conditions (such as hypertension and cardiovascular disorders), for which drugs are often taken on a long-term basis, patients have indicated that written information was useful in helping them understand their disease or the nature and use of their medication (Hladik and White, 1976; Clark and Bayley, 1972; Dwyer and Hammel, 1978; Kanouse and Morris, unpublished). Several studies examining the effects of written communications for a variety of drugs also have reported positive patient opinions about the information and its usefulness (Doyle, 1977; Namikas et al., 1976; Weibert, 1977; Romankiewicz et al.,

1978). In other studies of written information accompanying non-orally administered drugs (a Progestasert(R) IUD and a vaginal fungicidal cream), most respondents reported the written material to be instructive (Noyes and Gordon, 1975; Benson et al., 1977). In a Swedish study, a majority of patients receiving a drug information insert with their antibiotic medication indicated that they read the insert, and most reported positive opinions about its contents, value, and readability (Eklund and Wessling, 1976).

Favorable patient reactions also have been reported with FDA-required PPIs. Questionnaire responses from women receiving a PPI with estrogen postpartum indicated that a substantial majority of them found the insert useful and easy to read (Udkow et al., unpublished). Several surveys of oral contraceptive (OC) users have found them generally desirous of written information about the drugs, attentive to the material, and appreciative of its usefulness in answering some of their questions (Fleckenstein et al., 1976; Applied Management Sciences, 1975; Morris et al., 1977; Mazis et al., 1978).

There is also some scattered evidence that some patients make continuing use of written information about their medication. In a small survey of patients who had received an instruction sheet with prescription drugs in a program initiated by the Minnesota State Pharmaceutical Association, a majority reported that they had saved it (Weibert, 1977). In a small telephone survey of 22 cardiac patients who were contacted a month after discharge from the hospital, most indicated that they had retained the medication instruction information for their cardiovascular medications, and the majority indicated that they had referred to the information at home on more than one occasion (Hladik and White, 1976). Dwyer and Hammel (1978) reported that in their small sample of hypertensive patients who received PPIs, more than 60 percent of the subjects had kept the insert, and almost half of the patients reported that they had reviewed the PPI since receiving it, most often referring to it for specific purposes such as checking on drug side effects. Romankiewicz and his colleagues (1978) found that more than half of the patients who received "patient medication instruction cards" with their discharge medications reported that they carried the cards in their purse or wallet as advised. In a recent survey of oral contraceptive users, the PPI or brochure was reported to have been consulted by users for a variety of reasons, including what to do when they missed a pill, experienced some physical problem, or were unable to contact their physician (Morris et al., 1977; Applied Management Sciences, 1975). Preliminary findings from another study of patients who received a prototype PPI with thiazide drugs for hypertension indicated that most patients took it home, where 91 percent said that they had read the insert again. Sixty-six percent of the patients reported having shown the PPI to someone else, while 70 percent indicated that it had answered their questions (Kanouse and Morris, unpublished).

Concern has been expressed about the effects of PPIs on patients' willingness to use needed medications and their attitudes toward their

relationships with physicians. Although this has not yet been studied directly, Joubert and Lasagna (1975) present some interesting findings concerning some related aspects of patients' views of the doctor-patient relationship. When asked about preferred sources of information about prescription drugs, subjects indicated a preference for the physician as their main source of information. The PPI ranked second, and other information sources, such as medical reference books, medicine labels, and the pharmacist, were preferred by fewer respondents. It appears that patients desire information about prescription drugs and that the adequate provision of such information is an important ingredient in a satisfactory doctor-patient relationship. However, even patients who prefer the physician as an information source may see a useful place for the PPI.

The possibility has been raised that PPIs may affect patients' general attitudes towards drugs and their willingness to use medications. Some believe that PPIs will lead patients to appreciate more fully the risks of drugs, a matter about which some concern now exists. For example, an FDA survey found that consumers tended to view prescription drugs as safer than non-prescription drugs, commonly citing the reliability of the prescribing physician as the reason for their response (Knapp, 1974).

Concern also exists about the potential negative effects of PPIs on patients' morale and their attitudes toward their own health status. This is seen as a possible result of including extensive information in PPIs about possible risks and side effects. Similar concern has been expressed about the possible results of including information about the purpose of, or indications for, drugs. This, it is feared, may result in some patients drawing diagnostic conclusions (perhaps inaccurately)* that may diminish their psychological resources, or it may prompt physicians to make diagnostic disclosures that they might not otherwise make because of concerns about the possible psychological impact on the patient. These possibilities underlie the argument that, if PPIs are to be required, physicians should have the option of withholding them from patients. Whatever the resolution to that policy question, there are indications that physicians' attitudes toward disclosing diagnoses such as cancer may be changing, at least in major medical centers (Novack et al., 1979). Nevertheless, questions remain about the possible unexpected effects of certain diagnostic disclosures. For example, Haynes et al. (1978) recently reported how work absenteeism among steelworkers increased after hypertension was diagnosed. Among workers who were previously unaware of their hypertension a positive association was found between absenteeism and exposure to an educational program designed to increase their knowledge about hypertension and its treatment. These findings suggest that the education program might have augmented some negative effects of awareness about hypertension among these men.

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*A related concern, that drugs indicated for multiple conditions may lead to false (and disturbing) inferences by patients regarding their health status, also has been expressed. (See Morris and Kanouse, 1979.)

Because of the importance of patients' attitudes, several investigators have suggested that research on PPIs' effects on patients should be guided by theoretical models, such as the "health beliefs model" (Rosenstock, 1966; Becker, 1974) or "illness behavior model" (Mechanic and Volkart, 1961; Mechanic, 1978), which focus attention on patients' perceptions (regarding such matters as their condition and the efficacy of various courses of action) and the relationship of these perceptions to their behavior and health outcomes (Sharpe, 1977; Morris and Halperin, 1979; Christensen, 1978; Blackwell, 1976).

Cognitive Effects

One of the most obvious predicted effects of PPIs is that they will increase patients' knowledge. At present, studies of the educational effects of actual PPIs are less common than are studies of the impact of written prescription drug information provided to patients as part of a larger program of patient education. The usefulness of these latter studies, however, is limited by certain design features. In most cases the effects of the written information are not distinguished from the effects of the other aspects of the patient education program. Because the extent to which additional patient education generally will accompany PPIs is not clear, the separate effect of the written information is important to know. Another limitation of these studies is that the content and emphases of the written information provided to patients are not necessarily the same as would appear in required PPIs. The information given to patients in these studies tends to be directed toward narrow aims, such as improved "compliance with medical regimens," and includes less information about side effects and risks than PPIs may usually contain. Furthermore, the positive results of some of these studies, many of which are preliminary evaluations of demonstration projects, may be due to the novelty of the education program rather than to the program (or specific program components) itself. There are obvious dangers in using short-term impact as a long-term predictor.

These limitations notwithstanding, improvements in various areas of patients' knowledge have been observed in several studies of special educational programs designed to improve drug utilization by providing written information to patients about their disease, their medication and directions for its use, and the importance of compliance (Madden, 1973; Mattar et al., 1975; Clark and Bayley, 1972; McKenney et al., 1973; Sackett et al., 1975; Clinite and Kabat, 1976; Newcomer and Anderson, 1974; Romankiewicz et al., 1978). (These studies also show that it is easier to affect patients' knowledge than their compliance, a complex problem influenced by many factors besides knowledge.) Increases in patients' knowledge also have been reported from several studies in which patients were given written materials describing common side effects and special precautions or instructions for drug use (Eklund and Wessling, 1976; Weibert, 1976; Fox, 1969; Paulson et al., 1976; Boyd et al., 1974).

Much of this research provides support for the use of written information as a component of patient education programs; however, no evidence exists to support the use of written information as a substitute for oral counseling (Morris and Halperin, 1979). A few evaluations show PPIs or PPI-like materials in combination with oral instructions to be no more effective in improving knowledge than oral counseling alone (MacDonald et al., 1977; Jones and Russell, unpublished), and other studies suggest that some written communications by themselves may have limited or no effect on patients (Clinite and Kabat, 1976; Gray, 1975; Clark and Bayley, 1972). Overall, there is general agreement that the best educational effects will probably result from the use of both written and oral instruction.

Two recent studies have examined the educational effects of PPIs. Preliminary results of a study examining the effects of a prototype PPI for thiazides show the brochure was only partially successful in communicating important information to hypertensive patients. An increase in knowledge about thiazide drugs was found, but no significant differences were noted among experimental and control groups regarding knowledge about hypertension (Kanouse and Morris, unpublished). Preliminary data from a study on the impact of the required estrogen PPI on postpartum women shows that women who reported receiving and reading the PPI prior to estrogen therapy for suppression of lactation scored higher on a knowledge test about estrogens than did a demographically similar group of women who, for various reasons, did not receive or read the PPI (Udkow et al., unpublished).

Support for the educational role of PPIs can also be found in two retrospective surveys of oral contraceptive (OC) users and former users (Fleckenstein et al., 1976; Morris et al., 1977; Applied Management Sciences, 1975), which suggest that the PPIs accompanying OCs may have had a positive impact on patients' knowledge about OC use, although no comparisons were made with groups who had not received PPIs. Those surveyed were reasonably well informed about common side effects and directions for use, although there were variations in this regard; of course, patients may have gained knowledge through means other than PPIs (for example, through the mass media). In the study of a national probability sample, by Morris et al., more than 90 percent of OC users reported that they received a PPI and almost 90 percent of these users reported that they had read it. More than two-thirds of this latter group recalled the directions for use from the PPI, and almost half remembered the information about side effects. In the study by Fleckenstein et al., in which questionnaires were given to six subgroups of college students and clinic outpatients in the Rochester area, only about two-thirds of the OC users were aware of the PPI, but more than 90 percent of these had read it, and of these, almost 90 percent reported that it was useful to them. (Somewhat similar findings are reported by Ryan and McMahon (1977) in a study of a small sample of OC users in New Orleans; approximately two-thirds of the respondents indicated that they had received and read the PPI, with most reporting that the insert had benefitted them.) Most of Fleckenstein's PPI users were able to give correct answers to most questions

about possible side effects. Despite all of these findings, it is also clear that the educational usefulness of PPIs will be highly dependent upon the literacy of the recipient. Ryan and MacMahon, for example, found that PPIs had a much lower educational effect in a sample of Charity Hospital clinic patients (whose average schooling had ended at fifth grade) than in a more highly educated sample of patients at the Tulane University Medical Center (Ryan and MacMahon, 1977).

Among the most interesting findings of the study by Morris et al., was that patients preferred more extensive and detailed information about oral contraceptives. However, there were some indications that concisely stated information was perhaps more effective in communicating key points. The FDA requires that information regarding the risk of blood clotting be highlighted in a box in the OC PPI. Of the current OC users who had read the PPI, 54 percent recalled ("aided recall") the blood clot information if they were asked what information about side effects had been in the box in the PPI. Current users who said they had read a more detailed booklet about OCs were asked to recall ("unaided recall") its contents; about 32 percent mentioned the topic of blood clots. When specifically asked what the booklet said about blood clots, only 22 percent of the entire sample could recall (Morris et al., 1977; Applied Management Sciences, 1975). Since the questions regarding the contents of the PPI and the booklets were not strictly comparable, these negative results of more extensive information can at best be considered tentative.

Nevertheless, it is plausible to suggest that the structural features of written material, such as length, detail, format, and tone, might influence its communication impact. Only a few researchers have sought to compare such PPI characteristics. Clark and Bayley (1972) found that a "programmed instruction" booklet led to greater patient knowledge about warfarin therapy than an information sheet containing the same factual information. Benson et al. (1977) compared two information sources for the Progestasert(R) IUD, a company-prepared brochure and a proposed FDA PPI, which differed in content, organization, wording, length, and use of illustrations. Patients' comprehension of the two inserts was similar. In their study of a small sample of newly diagnosed hypertensive patients, Dwyer and Hammel (1978) found no evidence of significant effects on patients' responses of 'realistic' variations in the form of presentation and amount of detail of PPIs. FDA-supported research is currently under way in which several characteristics of PPIs will be experimentally manipulated to ascertain the sensitivity of the responses of different types of patients to differences in the way that important information is presented in PPIs.

A major concern about PPIs is that patients will have difficulty understanding them. The importance of readability and the validity of concern about it emerges from several studies. Ley and his colleagues (1976) found a direct relationship between the readability of three informational booklets and medication compliance in a group of psychiatric outpatients. Two recent studies, using standard readability formulas to analyze PPIs, have concluded that some patients will be unable to compre-

hend them. The estrogen PPI scores at the ninth to tenth grade reading level (Pyrczak, 1978), and prototype PPIs under study at FDA for thiazides and methyldopa, required reading comprehension skills at approximately the sixth grade level (Liguori, 1978). But there are millions of people who cannot comprehend materials at these levels. On the other hand, concern has also been expressed about how well-educated people may respond to materials aimed at poor readers.*

The blind application of readability formulas to assess patient drug information has come into question; although readability is important, there is also evidence that PPIs' interest, informational value, and believability are also likely to influence whether PPIs will be read (Morris et al., unpublished). Another variable is suggested by Sharpe and Mikeal (1974), who found in pretesting several drug information sheets with a group of predominantly lower income patients that type size (as well as the ease with which material can be read) should be considered in devising effective written information.

Concern has been expressed that patients may have difficulty evaluating the relative risks and benefits of drug therapy after reading the PPI and may become confused as to the appropriate course of action.** There is also concern that disclosure of risk information will unduly alarm patients and cause them to refuse needed medications; although it is also possible that patients' decisions not to use certain drugs, based on information in PPIs, may lead to the avoidance of very real negative consequences. Patient behavior in these areas is very complex and has not been adequately studied. Thus far, however, there is little evidence to suggest that information provided to patients will lead them to make "unwise" medical decisions.

Some information exists, however, about how written drug information may affect patients' decisions about medications. Two surveys of oral contraceptive users and former users found that women who take OCs and who read the PPI generally discontinue the drug in response to the experience

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* How best to reach "intended audiences" of PPIs requires additional research in the preparation of PPIs. Although not specifically addressed in this report, the committee viewed the matter of PPI design as very important. Poorly written and poorly structured PPI information may hinder effective communication and interfere with patients' ability to interpret risks and benefits and make rational decisions about drug therapy.

** For some useful concepts and interesting data regarding some general types of systematic errors commonly made by people in assessing probabilities and predicting outcomes in which factors of chance are involved, see Tversky and Kahneman (1974).

of actual side effects, rather than to the PPI warning (Fleckenstein et al., 1976; Morris et al., 1977; Applied Management Sciences, 1975). That patients in some situations will rely more heavily on personal experience than on written material is also suggested by a study in which a sample of medical school and hospital employees were asked to volunteer for a study in which they would have to take two tablets of "acetylhydroxybenzoate" or placebo the next time they had a headache (Epstein and Lasagna, 1969). Different consent forms were used in which the drug's hazards were described in increasing detail. Consent to volunteer was found to be inversely related to the length of the form (as was comprehension). However, when told that "acetylhydroxybenzoate" was actually aspirin, 20 of 21 who had refused to take it in the study indicated that they would continue to take aspirin as they had previously.

That study provides evidence that descriptions of risks may influence patient behavior. Because it pertained to a request for volunteering to participate in research, however, the study should not be interpreted as showing that patients will take actions that are against their own best interests. More direct evidence on this point comes from a study that the author acknowledged was undertaken to demonstrate that patients would make unwise decisions if provided with risk information (Alfidi, 1971). Alfidi began giving patients who needed angiographic procedures a consent form that described in detail the risks (including the risk of death) of the procedure. To his surprise only about 2 percent of the 232 patients in the study refused the procedure on the basis of the consent form. A substantial majority of the patients found the information provided to them to be "useful," and most indicated that such information should be available to all patients.

Two surveys in which the effects of risk disclosure were examined in populations receiving required PPIs found some inconsistency between patients' benefit-risk analysis and their use of a drug. Udkow et al. (unpublished) found that in a group of 71 postpartum women who were exposed to an estrogen PPI, about half gave a negative risk-benefit assessment to estrogen therapy; yet only five of these women refused estrogen therapy and only two based their refusal on the information in the PPIs. Fleckenstein and his colleagues (1976) also identified a group of patients who believed that the benefits from taking oral contraceptives did not outweigh the risk to their health, but who continued using the agent. This group represented about one-third of the current OC users in the study. Such results suggest that much is still not known about the role played by information in patients' decision-making processes regarding the use of drugs.

A final concern about the disclosure of risks and side effects of drugs pertains to situations in which few attractive therapy alternatives exist. Critics of PPIs have argued that the use of a PPI in such circumstances can cause unnecessary anxiety in patients. While such concerns should be considered in development of PPIs, existing research findings suggest that the problem may be less severe than some have feared. Kanouse and Morris (unpublished) found that a large majority of their

population of newly diagnosed hypertensive patients reported that exposure to a thiazide PPI did not upset them. In a similar, although much smaller patient population, Dwyer and Hammel (1978) noted that the amount of detail in a PPI had only negligible effects on treatment-related anxiety. On the other hand in the Alfidi study, which was undertaken to demonstrate patients' responses to an angiography consent form, 40 percent of patients responding to a questionnaire indicated that the information in the consent form had "disturbed" them and 17 percent said that they "would have preferred that information concerning possible complications" be withheld (Alfidi, 1971). However, the disclosure of risk in the Alfidi study was particularly stark, perhaps because the study was undertaken to demonstrate that disclosure of risks to patients will have negative effects; in a sense, therefore, the researchers set out to frighten the patients. Since PPIs will presumably have a more neutral intent, they may be less likely to disturb patients or prompt them to indicate that they would prefer not to have the information. Another point about which little is presently known is how patients who prefer not to have information will actually respond to PPIs—they may, for example, simply ignore them. Thus, it is difficult at present to draw firm conclusions about the extent to which PPIs will cause unnecessary anxiety in patients.

Patient Compliance in Medication

Many believe that the communication of information in PPIs will increase the probability that patients will take medications as intended by the prescribing physician. As has been noted, the counterpart of this effect—that disclosure of certain information about drugs will heighten patients' awareness and fear and lead to reduced following of medical advice—also has been predicted.

In the years since the "compliance problem" has come to light, many reports have been published of the impact of special patient education programs undertaken to improve compliance rates. Many of these programs have included written information about the prescribed drug and its proper usage. The results of these approaches to improving patient drug-taking are mixed, and design problems are a frequent feature of evaluation studies. The written information used in these programs varies in its form and mode of presentation (in isolation or in combination with other educational interventions), making comparisons across studies difficult. Similar problems are raised by the diversity of compliance definitions employed in this body of research. In theory, at least, "compliance" could include any or all of the following: getting the prescription filled, proper dosage at a given administration, proper schedule, proper timing, taking the drug for the proper amount of time or stopping at the proper time, not taking the drug if contraindicated, avoiding drug-drug and drug-food interactions or contraindicated activities, proper observation and reporting of signs and symptoms, or proper action for overdosage. Most studies of compliance have concentrated on medication errors of omission.

Several well-designed, experimental studies have shown that written prescription drug information can contribute to improved drug-taking behavior for short-term therapy with adults (Sharpe and Mikeal, 1974; Linkewich et al., 1974) and children (Colcher and Bass, 1972). Significant improvement in compliance with antibiotic therapy has also been found in other less well-controlled studies in which the written information was dispensed by a pharmacist (Madden, 1973; Lima et al., 1976; Mattar et al., 1975). On the other hand, a Swedish study in which every other patient received an informational enclosure with antibiotic medications found no differences in self-reported compliance (Eklund and Wessling, 1976).

For drugs used on a long-term basis by patients with chronic conditions, written information, either by itself or as part of a program, does not seem to be effective in producing significant improvements in medication adherence (Dwyer and Hammel, 1978; Kanouse and Morris, unpublished; Sackett et al., 1975; Hecht, 1974). Even where written drug information may have some utility in improving compliance, sustained effects may not be attained (McKenney et al., 1973).

Studies of the effects of written instructions for a series of miscellaneous drugs reveal results similar to those obtained in the research on long-term drug use. Investigations in both the U.S. and Britain have found that written instructions may be useful in insuring or augmenting the communication of important drug information to patients, which in turn leads to better drug-taking behavior (Beardsley et al., 1977; Wandless and Davie, 1977; Boyd et al., 1974). The lack of significant improvements in drug utilization in other studies, however, suggests that written informamation, by itself or even in combination with other educational interventions, may not necessarily affect medication compliance (MacDonald et al., 1977; Newcomer and Anderson, 1974; Clinite and Kabat, 1976).

Two studies in which drug use behavior was defined to include patients' proper observation and reporting of signs and symptoms have shown that written material may encourage the reporting of side effects and adverse reactions. In one study that involved the use of written information in conjunction with other educational strategies for multiple post-surgery drugs, patients who received special instructions differed significantly from control patients in knowledge of adverse drug reactions and in the reporting of such effects to their physicians. However, the groups did not differ in self-reports of the incidence of adverse drug reactions (Newcomer and Anderson, 1974; Newcomer, 1973). In a less well-controlled study in which hospitalized patients received written instructions with a variety of discharge medications, the percentage of study patients "who recognized side effects and reported to MD" was approximately 40 percent higher among those who received instruction cards than among control patients (Romankiewicz et al., 1978).* These studies

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* The data reported do not clearly distinguish between recognized and reported side effects; it is also unclear whether differences are in the experiencing or the attribution of side effects.

provide some support for the notion that disclosing information about risks, side effects, and potential adverse drug reactions in PPIs may have some positive effects. Patients may be able to assist in the early recognition and reporting of problems--thus reducing further adverse consequences--and patients' anxieties may be reduced when they know the possible side effects and how to interpret them if they occur.

Certain characteristics of written material may influence its effect on drug-taking behavior. In the study by Ley et al. (1976), in which groups receiving drug leaflets of three levels of readability were studied along with a randomly assigned control group of psychiatric outpatients, the group with the most readable leaflets had better medication compliance than groups given leaflets of moderate and difficult readability. The medication error scores of those patients receiving the difficult leaflets did not differ from the control group. On the other hand, when the form of presentation and the level of detail of patient package inserts were experimentally varied in a study of newly diagnosed hypertensive patients, results indicated that these variables had no significant effect on patient compliance (Dwyer and Hammel, 1978).

While this body of literature provides some foundation for the hope that PPIs will contribute to reducing problems of noncompliance, at least with some types of drugs, the limitations of these studies must be recognized. The studies vary in their methodological quality, in methods used, in conceptualization and measurement of compliance, and in other ways; they also share two limitations with the patient education studies that prevent the drawing of conclusions about PPIs. First, with notable exceptions (e.g., Kanouse and Morris, unpublished; Dwyer and Hammel, 1978; Weibert, 1977), most of these studies use written material that was drawn up specifically with drug compliance problems in mind. While the extent to which PPIs will contain material designed to improve compliance remains to be seen and may vary from drug to drug, it seems likely that such material will generally have less prominence in PPIs than in the written materials used in compliance studies to date. Second, in many of these studies the effect of the written material itself cannot be distinguished from the effects of the larger program to influence patients' behavior. Depending upon the way PPIs are distributed to patients (by physicians, by pharmacists, or as actual inserts in the drug packages that are opened at home), the extent to which PPIs are accompanied by verbal instructions is likely to vary. In a few studies, however, the effect of the written information on patients can be ascertained (Sharpe and Mikeal, 1974; Clark and Bayley, 1972; Eklund and Wessling, 1976; Kanouse and Morris, unpublished; Dwyer and Hammel, 1978; Ley et al., 1976; Clinite and Kabat, 1976).

Other Patient Behavior

Another set of predictions regarding possible effects of PPIs pertains to self-medication by patients. Although there is growing interest in self-care and in the possibility of improving it (Williamson and

Danaher, 1978; Levin et al, 1979), the fact remains that a defining characteristic of prescription drugs is the need for professional supervision in their use. Some people believe that providing patients with information in PPIs will encourage them to self-diagnose and self-medicate more readily and to share medications more freely. Harmful consequences are expected. However, two other arguments about PPIs and self-care have also been made. One is that PPIs, by warning against the dangers of self-medication and sharing of medications, will discourage such practices. The other is that self-diagnosis, self-medication, and sharing of medications are facts of life, that such behavior is quite appropriate in some cases, and that PPIs can serve an educational function and increase patients' competence in providing self-care (Green and Faden, 1977). Furthermore, it is argued, PPIs may help create a more informed public which may, in turn, expand consumer participation in health care and spur changes in the locus of control in provider-patient relationships (see also Howard and Tyler, 1975). Thus far, the general topic of self-care in medicine and health has received relatively little study, to say nothing of the possible role of PPIs. Clearly, however, self-care is a topic about which strong ideological views exist, which may account for the striking divergence of predictions about the possible role of PPIs.

An early FDA-sponsored consumer survey, in which general self-medication attitudes and beliefs were examined, offers some baseline information against which to assess the effect of PPIs on patients' willingness to self-medicate. Self-reported data indicated that, in general, "average" adult consumers follow physicians' recommendations, that the majority tend not to self-medicate common ailments beyond a week, and that most of those experiencing more serious problems receive advice and treatment from physicians (Knapp, 1974). In the one study that investigated in any detail the potential of medication errors of this type, counseling was shown to be useful in reducing the use of old medications and other people's medicines in a group of geriatric patients after discharge from a British hospital; however, three types of memory aids were, at best, of limited usefulness in further improving patient behavior (MacDonald et al., 1977).

Another concern is that the provision of drug information, particularly regarding risks and indications for use, will lead to increased patient demand on physician or pharmacist time to obtain further information, reassurance, or additional or substitute prescriptions. At present, the only data that bear on this question are from the Morris et al., (1977) survey of oral contraceptive users. No substantial change in physician-patient contact could be attributed to the OC PPI or booklet, but where changes were reported by patients, they tended to be reduced contact.

Health Outcomes

Several types of health outcomes have been predicted for PPIs, and several mechanisms have been posited by which PPIs may affect therapeutic outcome. It has been predicted (a) that PPIs will improve

compliance, thereby increasing the therapeutic effectiveness of drugs, (b) that PPIs will reduce the therapeutic effectiveness of drugs by interfering with the beneficial actions of the placebo effect, (c) that PPIs will reduce the incidence of adverse reactions by providing patients with necessary warnings and instructions, (d) that PPIs will increase the incidence of adverse reactions through suggestion, (e) that PPIs will cause patients to attribute symptoms experienced to the drug, thereby producing an apparent increase in adverse reactions, (f) that PPIs will prepare patients for the predictable and benign symptoms that the drug may produce, thereby increasing the probability that they will continue using the drug once the symptoms develop, and (g) that PPIs may warn patients about using certain drugs that may be harmful, thus resulting in long-term health benefits. In this section, all of these types of potential PPI impacts on therapeutic outcome are discussed.

In a few compliance studies direct measures of therapeutic outcome have been used in addition to the more common measures based upon pill counts and patients' self-reports. With the exception of the Kanouse and Morris research, however, these studies share the twin problems of using written material that was (a) designed primarily with the compliance problem in mind, and (b) used in combination with other interventions. These limit the validity of extrapolating results to PPIs. Among the therapeutic outcome measures in which written materials have been associated with improvements are the blood pressure of patients receiving antihypertensive drugs (blood pressures returned to earlier levels after the five-month study phase, however) (McKenney et al., 1973), hospital readmissions of cardiac patients (Rosenberg, 1971), and relapses in children with strep throat (Colcher and Bass, 1972). On the other hand, in the Sackett et al. (1975) study of compliance and the effectiveness of antihypertensive drugs in a sample of steelworkers, no effect on compliance or blood pressure was found, despite improvements in patient knowledge. Kanouse and Morris (unpublished) have reported similar preliminary results in a group of newly diagnosed hypertensive patients; no significant effects in blood pressure (or self-reported compliance) were found in response to a prototype PPI for thiazide drugs.

The effect of PPIs on the quality of care (or on patients' satisfaction with it) has not been studied. Empirical assessment also is lacking on the possible impact of PPIs on the placebo effect. It has long been recognized that there are non-specific effects of treatment that occur frequently and may improve therapeutic outcome (Shapiro and Morris, 1978; Jospe, 1978; Morris and Kanouse, 1979), and an extensive literature exists on psychological suggestability (Holmes, 1976a; Holmes, 1976b; Ross et al., 1975; Schachter and Singer, 1962). While this research lends plausibility to concerns about PPIs and placebo effects, understanding of the mechanisms involved in the placebo effect remains limited and little information exists about the possible impact of PPIs on it.

Regarding the potential impact of PPIs on the incidence of adverse reactions and side effects two viewpoints exist. Some believe that PPIs may play a role in preventing adverse reactions by informing patients

about proper usage of drugs, warning signs, and so forth; however, there is no evidence, other than an occasional anecdote, for this potential benefit of PPIs. On the other hand, some fear that disclosures in PPIs may increase the incidence of suggestion-induced side effects. This fear, though plausible, has not yet found empirical support in the literature on PPIs and similar written materials. In the few studies of this question, no differences have been found in self-reports of side effects between groups receiving and not receiving written information in which side effects are listed (Weibert, 1977; Paulson et al., 1976; Newcomer and Anderson, 1974; Newcomer, 1973; Kanouse and Morris, unpublished). Dwyer and Hammel (1978) studied the effects of three different levels of information presentation for an antihypertensive drug; patients randomly received either (a) a PPI that contained a description of expected side effects, (b) a PPI that described these side effects and instructed the patient of actions to take if they developed, or (c) a PPI that described the side effects, instructed the patient, and described the reasons why the side effects might develop. No significant difference was found in the incidence of side effects in the three study groups.

Although suggestion is the mechanism usually cited in predictions of increases in the incidence of side effects, some believe that PPIs may produce an apparent increase in the incidence of side effects by making patients aware of signs and symptoms they might otherwise ignore or not attribute to the drug (Morris and Gagliardi, 1977). Some support for this idea comes from preliminary results of a study by Kanouse and Morris (unpublished) who found that patients who received PPIs were more likely than other patients to attribute experienced side effects to the drug. Some related evidence comes from research in Britain on the effect of oral forewarning on the reported incidence of side effects and the discontinuance of medication. Psychiatric patients, for whom an antidepressant, Dothiepin (doxepin hydrochloride), was prescribed were alternately allocated to one of two groups; patients in one group were forewarned about the drug's side effects and those in the other were not. Forewarning patients neither increased their reporting of side effects nor caused more frequent discontinuance of the drug (Myers and Calvert, 1976). In an earlier study of depressed patients prescribed amitriptyline, the same researchers obtained similar results (Myers and Calvert, 1973). More recently Myers and Calvert (1978) report additional research of similar design with depressed patients: forewarnings of side effects again did not increase the incidence of reported side effects; however, patients receiving written information about side effects were significantly less likely to discontinue medication than were patients receiving oral or no information. This suggests that PPIs may play a useful role for patients who experience side effects.

Even if PPIs cause an increase in the incidence or perception of side effects, this would not necessarily be bad. The experience of certain side effects may act to assure patients that the medication is working, provided that the patient has been told to expect the effect (Shapiro and Morris, 1978; Morris and Gagliardi, 1977).

One other type of possible therapeutic benefit of PPIs is their potential indirect impact on the prescribing of certain drugs. Estrogen prescribing in menopause illustrates an instance. Epidemiological studies published in 1975 revealed an association between the incidence of endometrial cancer and the prolonged use of post-menopausal estrogens. Soon thereafter, congressional hearings were held regarding this finding, and the FDA issued a drug bulletin warning about the risk of estrogen use. New physician labeling for post-menopausal estrogens was mandated in early 1976 and, in October of 1977, regulations were promulgated requiring that a PPI accompany all prescribed estrogen products (Burke et al., 1978, mimeo). Nationwide estrogen use declined by 18 percent from 1975 to 1976, and by 10 percent more from 1976 to 1977 (FDA Drug Bulletin, 1979). The incidence of endometrial cancer also fell during this period. Jick and his colleagues estimate the decline to be about 27 percent nationwide (FDA Drug Bulletin, 1979). Thus, there is a strong temporal association between the decline in dispensed estrogen prescription levels and the decrease in the reported incidence of cancer. While a specific effect of PPIs cannot be distinguished and no clear cause-and-effect relationships can be established, these data suggest a research strategy by which prescribing trends for other drugs of questionable use or overuse, both before and after the introduction of a PPI, might be compared.

Predicted Effects on Physicians

Physicians' Attitudes

Although no studies have been conducted on the effects of the use of PPIs on the attitudes of physicians, a number of surveys have been carried out to assess their views of PPIs. Some low response rates and various sampling limitations notwithstanding, several of these surveys report finding considerable support for the concept of PPIs among physicians (Ryan and McMahon, 1977; Noyes and Gordon, 1975; Fleckenstein, 1977). (In their New Orleans sample, which included all physician specialties, Ryan and McMahon found that a majority of respondents indicated that they were opposed to the "routine use" of PPIs, but that they would favor the concept if they were given discretion in indicating on prescriptions that particular patients should not receive a PPI.) Many respondents, however, expressed concerns about PPIs, usually that patients would be confused or upset by the information they receive. The results of other surveys are less positive. A Patient Care survey of primary care physicians found that respondents were divided about the potential benefits of PPIs, with skeptics of the concept in the majority (Wickware, 1977). Of the 100 specialists in obstetrics and gynecology contacted in a survey conducted by Medical Economics, 61 percent opposed extending PPIs beyond oral contraceptives (Carlova, 1974).

In two of these surveys physicians were specifically asked for their opinions about possible effects of PPIs on their relationships with patients. Fleckenstein (1977) found that most respondents did not perceive the PPI as interfering with the physician-patient relationship.

A majority of the obstetricians and family practitioners surveyed by Noyes and Gordon (1975) agreed that a model vaginitis information leaflet for patients would save physicians' time because patients would ask fewer routine questions.

Physician Behavior and Knowledge

A number of predictions have been made regarding changes that PPIs will bring about in physicians' behavior. Some expect PPIs to provoke questions by patients, causing physicians to increase the amount of information provided to the patient when the prescription is written; others fear that physicians will rely on the PPI to communicate necessary information to patients and will reduce their oral communication. Another area of predicted change, as was noted earlier, pertains to physicians' prescribing practices. If PPIs contain information about drug effectiveness, the prescribing of drugs of questionable efficacy may be reduced. A similar effect may occur with some drugs on the basis of risk. Some changes may result if patients become more aware generally of the risks of drugs and change their expectations that an office visit should produce a prescription. Some changes may result from physicians' attempts to avoid drugs that have PPIs, either because they believe that the PPI contains information that might unnecessarily alarm patients or prompt unwanted questions, or because of concerns about liability (as with a drug prescribed for an unapproved purpose). Some expect that physicians will narrow the variety of drugs that they prescribe, restricting themselves to those about which they are most knowledgeable and most prepared to answer questions. Changes in referral patterns have been predicted for similar reasons. Finally, there have been predictions that PPIs will have an indirect effect of making physicians more knowledgeable about the drugs that they prescribe, either as a result of, or in preparation for, questions by patients.

All of these predicted changes in physicians' behavior and knowledge are empirically testable, but they have not yet been directly addressed in research on PPIs.

Additional Effects on the Health Care System

Roles of Other Health Professionals

The PPI may bring changes for health professionals other than physicians, particularly pharmacists and nurses. Within both nursing and pharmacy, there has been great interest in recent years in expanded responsibilities and increased professionalization. In nursing, such efforts are reflected in the development and growing acceptance of the nurse-practitioner as a provider of primary care (Institute of Medicine, 1978). In pharmacy, great interest has developed in the movement toward clinical pharmacy, a concept which would expand the role of the pharmacist as an integral member of the health care team who is involved

actively in patient care (Study Commission on Pharmacy, 1975). In both occupations, but particularly in pharmacy, the PPI is seen as providing a means for greater clinical involvement and increased professionalization. Since patients are to receive information in the PPI, patient counseling activities by pharmacists or nurses will be less inhibited, it is said, by uncertainty about what the responsible physician might or might not want communicated to the patient. Thus, the PPI is seen as defining and expanding the topics that pharmacists or nurses can legitimately discuss with patients. Preliminary data from a current study of pharmacists supports the idea that the use of PPIs will enhance the patient-counseling aspects of the pharmacists' role (Weibert, 1977; Letter from Robert Weibert, 1979).

Interest among pharmacists in PPIs is reflected in the fact that much of the research on the effects of written drug information on patients has been conducted by pharmacists. There are also, however, some concerns about possible effects of PPIs. Although existing surveys of pharmacists' views about PPIs are few in number and tend to have low response rates and selective samples, it appears that pharmacists' major concerns pertain to the possibility that PPIs will confuse patients (who are then likely to increase their demands on pharmacists' time) and increase costs (Ryan and MacMahon, 1977; Fleckenstein, 1977).

A number of state pharmaceutical associations have voluntarily developed written drug instructional materials to be used by pharmacists in conjunction with oral counseling. A number of other states, through state pharmacy laws and regulations, have mandated that pharmacists provide patients with drug information, disseminated orally or in writing, to help assure safe and appropriate medication use (Evans, 1977). Data collected on approximately 200 randomly selected pharmacies in Washington State reveal, however, that many pharmacists may not be counseling patients, even though oral explanation of directions for drug use is required. Results of a study in which senior pharmacy students posed as patients indicated that about 80 percent of the pharmacists met with patients and were willing to answer their questions, but only 47 percent explained the directions for drug use (Campbell and Grisafe, 1975). At present, much of the evidence about individual state drug information initiatives is general and anecdotal. A few states, such as Minnesota, have begun to evaluate their programs through community pharmacist-patient surveys (Weibert, 1977; Weibert, Letter from Robert Weibert, 1979).

Although no published survey data of nurses' attitudes regarding PPIs were found by the committee, the recent "Position Statement on Consumer Package Inserts" of the American Nurses' Association, Congress for Nursing Practice, advocated the use of "consumer package inserts" on all pharmaceuticals as one method of providing accurate drug information to improve consumer education and consumer decision-making concerning health care (American Nurses' Association, 1979). A few studies have examined the effects of nurse-dispensed drug information materials on patient knowledge and compliance (Hecht, 1974; Clark and Bayley, 1972; Hladik and White, 1976; Deberry et al., 1975). The authors of a more

recent study, in which patient drug information was provided by nurses, comment that nursing personnel proved to be a useful patient education resource in their hospital (Romankiewicz et al., 1978). A review of several studies, where nurses worked with patients to promote such health behaviors as better medication adherence, led one nurse researcher to suggest that nurses should be accorded a comprehensive role in patient counseling and distribute patient drug information and reinforce the PPI (Swain, 1977). Nurses, like pharmacists, may perceive PPIs as enhancing the development of certain aspects of their role. At present, no research is known to bear directly on the question of how PPIs may change nurse-patient relationships, and the committee found no studies that compared the distribution of PPIs by nurses or pharmacists with distribution by physicians.

Cost

PPIs have been predicted to increase health care costs because of (a) costs of preparation and distribution, (b) increased demands on professionals' time and (c) noncompliance and lessened drug effectiveness. PPIs have also been predicted to decrease health care costs as a result of (a) better therapeutic outcomes, (b) less drug wastage because of proper dosing and storing by patients, and (c) less use of marginally beneficial drugs. To date, however, no studies are available on the economic consequences of PPIs. Patient prescription drug labeling is still new and has been limited to a few drug agents, and its effects on health care costs have not been empirically assessed.

Some very rough predictions of potential direct and indirect costs can be calculated from the current OC and estrogen PPI experience. For example, the FDA's inflation impact assessment suggests that the direct costs of printing, distributing, and storing estrogen PPIs appear to be relatively small. An estimated figure of $2.4 million per year, which includes "marginal" increases in costs resulting from the need for increased pharmacy space, is believed by the Commissioner to approximate the direct cost based on current estrogen drug use rates (Federal Register 42, 1977).* The American Society of Hospital Pharmacists has estimated that a "given" hospital (with 250 beds; 80 percent occupancy rate; average patient stay of 7 days; unit of dose drug distribution system; and an average of 8-10 drugs per patient) would have to store and dispense over 100,000 "first dose" inserts and spend approximately $100,000 per year for

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* Although the major organizations representing pharmaceutical manufacturers, pharmacists, and drug stores have expressed concern over the cost of preparing, distributing, and storing PPIs, these groups could not make available to the committee any cost figures from currently required PPIs or estimates of the cost of expanded PPI requirements.

a PPI program.* Aside from the costs directly associated with PPI distribution, the Society predicts that overall systematic PPI use in an inpatient setting would require manpower distribution and time adjustments, with the potential for further increases in cost (American Society of Hospital Pharmacists, 1979).

The concern that the increased use of PPIs cause patients to ask more questions and demand more physician or pharmacist time has not been confirmed by the limited available research. The oral contraceptive PPI apparently caused no increase in patients' contact with their physician (Morris et al., 1977; Applied Management Sciences, 1975). Because the labeling required thus far has specifically suggested that patients direct their questions to prescribers, increases in patients' demands on pharmacists have probably been minimal.

At present, no cost-benefit analyses are available because of the paucity of quantifiable cost data and the lack of data on the intended or unintended effects of actual PPIs. More careful estimates of cost are needed. The committee, however, doubts the wisdom of evaluating the health and patient satisfaction benefits of PPIs in monetary terms. Rough estimates of the relative costs and benefits of various health education strategies have been offered and may prove useful in considering possible PPI cost-benefit ratios. For example, Green (1976) identifies the use of written materials as among the "low unit-cost measures" for health education, and considers how such factors as patient characteristics, disease state, and the health care context in which the materials are used may influence their effectiveness.

Other Extended Effects

A variety of less immediate effects of PPIs also have been predicted. The long-term widespread use of PPIs is seen by some as likely to affect (a) the degree of egalitarianism, reciprocity, and collaboration in the physician-patient relationship, (b) the self-care propensities of a more informed public, (c) the relationships among health team members and the counseling role of pharmacists and nurses, (d) the utilization of "unit-of-use" drug distribution, (e) the physical layout and functional capacities of community pharmacies, and (f) professional and manufacturer liability.

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* The regulations mandating patient labeling for prescription estrogenic drug products for general use (Federal Register 42, 1977) require PPI distribution in acute care hospitals or in long-term facilities before the administration of the first dose of estrogen and every 30 days while the therapy continues.

Summary

Although studies and surveys indicate that patients want written information about the proper use and possible hazards of the prescription drugs they use, and that patient reaction to PPIs they have received has been quite positive, data on the actual effects of PPIs are limited.

The use of written information to promote patients' knowledge and compliance with therapeutic regimens has been studied frequently, but results are mixed. Some success in using written information to improve compliance with drug regimens for acute illnesses has been reported, but the impact of written information on compliance with long-term therapeutic regimens has been minimal. However, because many of the studies do not distinguish the separate effects of the written information from the effects of the larger health education programs of which it is a part, and because the written information used probably differs in tone and content from actual PPIs, the usefulness of this literature for predicting the effects of PPIs as they are actually used in ordinary medical practice is limited.

Some results, however, are being reported from recent experimental studies of the effects of actual PPIs. These data indicate that patients generally read PPIs and find them useful and that PPIs may have some positive effects on their knowledge. Existing evidence does not support the contention that PPIs will increase the incidence of side effects or increase the demands of patients on health practitioners. Additional experimental studies are presently underway.

Little research has been conducted to date on the ways that PPIs are actually distributed and used in natural settings and the extent to which they affect practitioner-patient relations. The possible effects of PPIs on practitioners' attitudes and behavior--particularly their communication patterns with patients and their prescribing habits--have received little attention. The same is true of the possible impact of PPIs on the roles of the pharmacist or the nurse. Adequate estimates of the costs associated with the development and use of PPIs are also unavailable. No data are yet available on any long-term changes that may be associated with the use of PPIs or the extent to which short-run changes will prove stable over time. A framework for research on these and other effects of PPIs is described in Chapter 3.

CHAPTER 3

Research Needs for PPI Evaluation:

Analysis and Conclusions

This chapter presents an analysis of the possible effects of PPIs as a regulatory requirement and describes the research approaches the committee recommends to assess these effects. The various considerations that should underlie decisions regarding priorities and methods for evaluating the effects of PPIs are discussed initially.

In the deliberations leading to its conclusions, the committee worked from several basic premises that set boundaries for its inquiry. Because these premises affected the focus and content of this report they should be explicitly stated.

The fundamental presuppositions under which the committee worked are that there will soon be a regulatory requirement for PPIs with prescription drugs, and that the effects of such PPIs should be studied. FDA has made known its intention to issue regulations for this purpose and has undertaken a series of activities to that end.* The committee's task was to make recommendations about priorities and methods for the evaluation of the effects that may result from the more widespread use of PPIs. The committee did not focus on the question of whether the federal government—either through the pending regulatory actions at FDA or through new legislation—should require that PPIs be provided to patients with prescription drugs. Nor did the committee undertake any specific examination of such policy questions as how PPI requirements should be implemented, what PPIs should contain, who should develop PPIs, or how they should be distributed or

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* These are described in Chapter 1. The committee's deliberations and the drafting of this report were largely completed prior to the publication of FDA's proposed regulations for PPIs, although those proposed regulations were expected by the committee.

kept current. Nevertheless, the findings from the research activities recommended by the committee should bear on these questions and should provide insights about the wisdom of the basic assumptions and initial implementation steps of FDA's PPI program and the desirability of changes in that program.

The committee's understanding of the general outlines of FDA's plans for PPIs contributed to its thinking about research needs. However, during its deliberations the committee did not have information about the precise nature and details of these plans. Thus, FDA's forthcoming regulatory requirements may contain elements that were not anticipated by the committee, possibly raising a need to augment the committee's current recommendations for evaluation efforts.

The committee assumed that, no matter what other purposes PPIs may have, at minimum they will be designed to meet patients' desires and needs for information about the purpose, proper usage, and side effects of prescription drugs, and will be intended to present this information in a way that will be understandable to most readers. The committee assumed further that PPIs will not be what has been described as a "full disclosure" document in which all risk contingencies, however remote, are described; instead, the committee anticipated that the discussion of risks in PPIs will be confined to those of importance, by virtue of seriousness or high likelihood, and that patients will be informed how to obtain additional information. The committee also anticipated that FDA will make genuine efforts to maximize the acceptability of PPIs to patients and practitioners. This implies a number of steps. It was apparent at the committee's public meeting that medical practitioner and specialty groups, pharmaceutical organizations, and drug manufacturers will be more supportive of and cooperative with the PPI program if they have a role in the development and preparation of PPIs. Efforts should also be made to learn from consumers what information they would like to have included in PPIs,* to use communication specialists and graphic designers to make PPIs attractive, readable, and understandable, and to pretest PPIs to make sure that they meet patients' needs. Careful attention should be given to questions about the possible impact of PPIs on the liability of manufacturers and practitioners, and efforts should be made to anticipate the ways in which concerns about liability may shape manufacturers' and practitioners' responses to PPI requirements. Finally, there should be recognition both of the limitations of PPIs as a communication device and of the potential for increasing their effectiveness by making them part of a larger program that

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* Some research on this topic is presently being conducted under the direction of Seymour Fisher, M.D., at the University of Texas Medical Branch at Galveston. Actual patients are to use a card-sorting technique to indicate the categories and bits of information that they wish to have about the benzodiazepines (hypnotics) and tricyclic antidepressants. If successful, this research could provide a useful model for use in the construction of other PPIs.

includes, for example, the use of the mass media to increase patients' awareness of PPIs and their purpose, and educational efforts directed at increasing practitioners' understanding of PPIs and sophistication in their use.

FDA intends to require that PPIs be distributed with the drug when it is dispensed. However, some PPIs may contain information that would be relevant to patients' decisions about whether they want to use a particular drug, as is the case with oral contraceptives. The committee believes that ways can and should be developed to provide patients with information at the most opportune time, as with the brochures for oral contraceptives that several pharmaceutical companies have provided for distribution by physicians. However, in coming to its conclusions regarding evaluation, the committee has not assumed that PPIs will generally be provided to patients in advance of their purchase of prescription drugs, although the committee believes that the mode of distribution of PPIs will influence their effects and should be incorporated in research on PPIs. (The use of educational materials other than FDA-required PPIs should also be examined in such research.) Finally, the committee has assumed that regulations requiring PPIs will be implemented gradually. This will provide an opportunity both for experimental approaches to the study of the effects of PPIs that have not yet been required and for more naturalistic studies of the way PPIs that have been required are actually distributed and used in ordinary practice situations. The use of educational materials other than FDA-required PPIs should also be examined in such research.

The committee was asked to plan specific objectives and methodologies for evaluating the effects of FDA-required PPIs. The committee has taken this to mean that its primary concern was to consider how to evaluate the effects of PPIs as they are actually used, and little consideration has been given to such important topics as basic research on processes of comprehension and utilization of information.

An additional premise of the committee's deliberations concerns the audience for and purpose of this report. This project was undertaken by the Institute of Medicine at the request of the Food and Drug Administration. As with all Institute projects, however, the potential audience for this report goes well beyond the sponsoring agency and includes public interest groups, health services researchers, the pharmaceutical industry, professional associations in the health professions, foundations, and others who are interested in health care policy. The FDA's primary interest is in research that will contribute to future policy decisions in its PPI program. Clearly, this is an important and legitimate reason for evaluating PPIs. Yet, the committee recognizes that the establishment of a program that will provide information to millions of patients presents a more far-reaching occasion for research. Studies of the wider ramifications of this regulatory action by a federal agency may contribute to our general understanding of the social organization and politics of health institutions and occupations, and the complex processes by which requirements from a central authority are translated, shaped, and modified as they are applied in the real world. Rare is the program of regulation that is implemented as designed.

The committee strongly believes that answers to many of the questions that have been raised about the possible effects of PPIs can be provided by research and will be quite useful in future policy decisions. However, policy questions regarding PPIs involve more than the answer to any specific empirical question or set of questions. People who disagree about whether FDA should require PPIs may be expected to disagree also on the criteria by which the relevant policy decisions should be made. Some believe that the costs that will be associated with PPIs must be justified by measurable improvements in the health of patients or by reductions in the incidence of adverse reactions; the belief that PPIs must be justified in such terms is undoubtedly a source of skepticism about PPIs. Others believe in the right of patients to have readily available certain basic information about the drugs they use. Individuals and groups of that opinion might find the cost of PPIs justified if the information they contain is useful to one patient in a hundred. The point here is not to state what weight of evidence should suffice to justify FDA's PPI program, but to acknowledge the role and limits of empirical information in making decisions that are in substantial part a matter of values.

Analysis of Potential Effects of PPIs

In considering the evaluation of PPIs, the committee reviewed published opinion about the possible consequences of PPIs and held an open meeting at which the views of interested members of the public were heard. A wide variety of effects have been predicted for PPIs. These predictions provided a starting point for consideration of a research agenda for evaluation of the effects of PPIs. Many of these predictions, which often reflect the particular interests and biases of those offering them, are quite contradictory. For example, it has been predicted both that PPIs will improve the effective use of drugs by informing patients of correct usage, and that PPIs will frighten or confuse patients, who will then not use medications for which there are sound indications. Similarly, it has been predicted both that PPIs will reduce the incidence of adverse reactions by informing patients about necessary precautions in their use of drugs and that PPIs will increase the incidence or perception of side effects by suggesting to patients what side effects to expect. It has been predicted both that PPIs will prompt physicians to have more extensive discussions with patients about drugs being prescribed, if only to prevent the anxious question over the telephone, and that PPIs will come to replace doctor-patient communication. It is predicted both that PPIs will cause patients to demand more time from physicians or pharmacists to obtain answers to questions raised by the PPI, and that PPIs, by providing desired information, will reduce the number of questions raised by patients.

The conflicts in the predicted effects of PPIs may be more apparent than real, however. Opposing predictions may prove to have validity, since some effects of PPIs may vary according to the characteristics of the drug, the attitudes of the prescriber, the types of patients using the drug, the settings in which the drug is prescribed and used, the content and tone of the PPI, and so forth. In the committee's view, the planning of research will not be guided adequately by the expectation of

learning which of a pair of conflicting predictions is correct. Instead, the goal should be to identify the circumstances under which predicted effects do or do not occur. Thus, care must be taken to examine the use of PPIs in a variety of settings and with different types of drugs, practitioners, and patients. Almost all effects that have been predicted for PPIs may prove to occur with some patients and some drugs under some circumstances.

In considering the divergent predictions that have been made about potential effects of PPIs, and the research literature summarized in Chapter 2, the committee found that the possible objects of evaluation studies fit into a limited number of categories:

1. Patients' cognitive and attitudinal responses
2. Patients' behavioral responses

    a. Decisions regarding whether to use drug
        (1) Initially
        (2) Under various circumstances (for example, when taking other drugs, in combination with certain foods and drink, and when engaging in such activities as driving or vigorous exercise)

    b. Use of drug as intended by provider
        (1) proper dosage and course of therapy
        (2) proper precautions and monitoring of side effects
        (3) self medication

3. Incidence or perception (and attribution to drug) of side-effects or adverse reactions
4. Therapeutic outcomes
5. Doctor-patient relationship and communication
6. Physicians' attitudinal responses
7. Physician's prescribing and referral behavior
8. Pharmacists' role (attitudes, duties, and relationships)
9. Nurses' role (attitudes, duties, and relationships)
10. Cost
11. Liability
12. Broad "systems effects" in the organization and delivery of health care.

In addition to research that might link PPIs with the factors listed above, descriptive information is needed about how PPIs are actually used, as is discussed later.

Factors in Evaluation Strategy

In considering the variety of possible effects of PPIs, the committee concluded that several important points and distinctions bear on evaluation strategies.

Interrelationships of PPI Effects

A simple listing of potential effects of PPIs conceals the fact that these hypothesized effects bear a complex relationship to each other and to the PPIs themselves. Some effects of PPIs may be mediated by other effects. For example, patients' cognitive and attitudinal responses to PPIs may be affected both by the PPI itself and by their communication with health care providers about it. The potential effect of PPIs on patient compliance or on the occurrence of side effects may be influenced by several sets of factors, of which the PPI itself is but one. Furthermore, the relationship between any of these sets of variables is likely to be influenced by the characteristics of the physician (for example, specialty), characteristics of the patient (age, education, socioeconomic status, medical condition), the type of setting in which the care is provided, and so forth. Although complex interrelationships may link PPIs and possible outcomes of their use, in the committee's view the doctor-patient relationship and patients' responses should be central to the assessment of PPIs.

The complexity of interrelationships between variables must be carefully considered in the planning of evaluation studies. For example, hypotheses have been offered that PPIs will affect therapeutic outcomes. However, it is apparent that any such relationship will be mediated by other variables, particularly changes in prescribing and drug use patterns and patient compliance. Considered from this standpoint, the questions important to the evaluation of PPIs are whether and how they affect prescribing patterns, patients' use of drugs, and compliance with therapeutic regimens. The further questions about whether changes in prescribing, drug use, or compliance produce changes in therapeutic outcomes are not, strictly speaking, questions about the effects of PPIs; they are questions about the risks and benefits of drugs. If a relationship between patient compliance and therapeutic outcome is known to exist or can be assumed, it is not necessary to include therapeutic outcome in studies of the effects of PPIs on compliance.

Planned and Unplanned Effects of PPIs

In considering the possible effects of PPIs, the results expected if PPIs work as planned can be distinguished from those that will occur if the planned sequence of which PPI is a part goes awry. Figure 1 shows an intended sequence of events beginning with the patient's receipt of a PPI and ending with an improvement in the patient's health. Six elements are involved in this sequence, however, and reality can depart from the intended sequence at any stage. Figure 1 also illustrates some of the logical possibilities for such departures.

The sequence of events becomes more complicated when the physician's behavior is added. Figure 2 shows a more extensive ideal sequence beginning with the physician's diagnosis and ending with improvement in the patient's health. Again, complications will undoubtedly develop to produce departures from the ideal process.

An adequate evaluation of PPIs must recognize the key steps in the process by which PPIs may have an intended or unintended effect. Figures 1 and 2 make clear that questions such as whether patients receive PPIs, whether they read them, and whether they understand them are fundamental to the evaluation of PPIs, since negative answers to these questions can preclude any changes in behavior or health status as a direct result of PPIs.

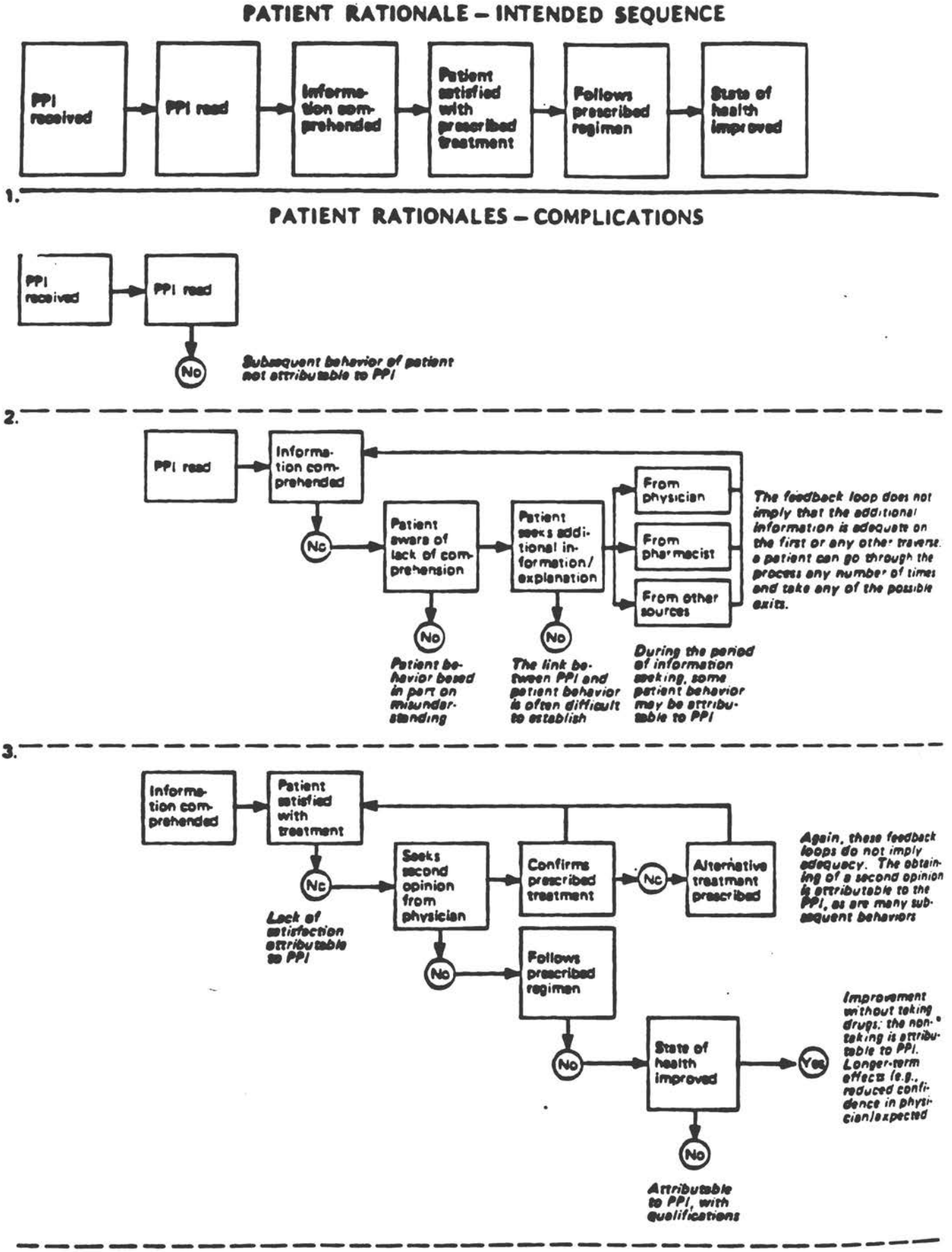
Evaluation and the Purpose of PPIs

An additional point must be made regarding the purpose of PPIs, strategies for evaluation, and interpretation of results. Although, as has been stated, the committee strongly believes that evaluation efforts must focus in substantial part on the less obvious and unintended consequences of PPIs, the question of whether PPIs accomplish their manifest purposes is also of great importance. A problem with attempting to focus research on this latter question, however, is that much confusion and disagreement exists about PPIs' purpose. Some see PPIs' purpose as pertaining to the "compliance problem" with some types of drugs (for example, oral antibiotics). Some see the purpose as providing patients with information that might help lower the incidence of certain adverse reactions or interactions. Some see the purpose as contributing to certain changes in present prescribing practices. Still others see the purpose as increasing patients' involvement in medical decision-making. Clearly, PPIs may serve multiple purposes.

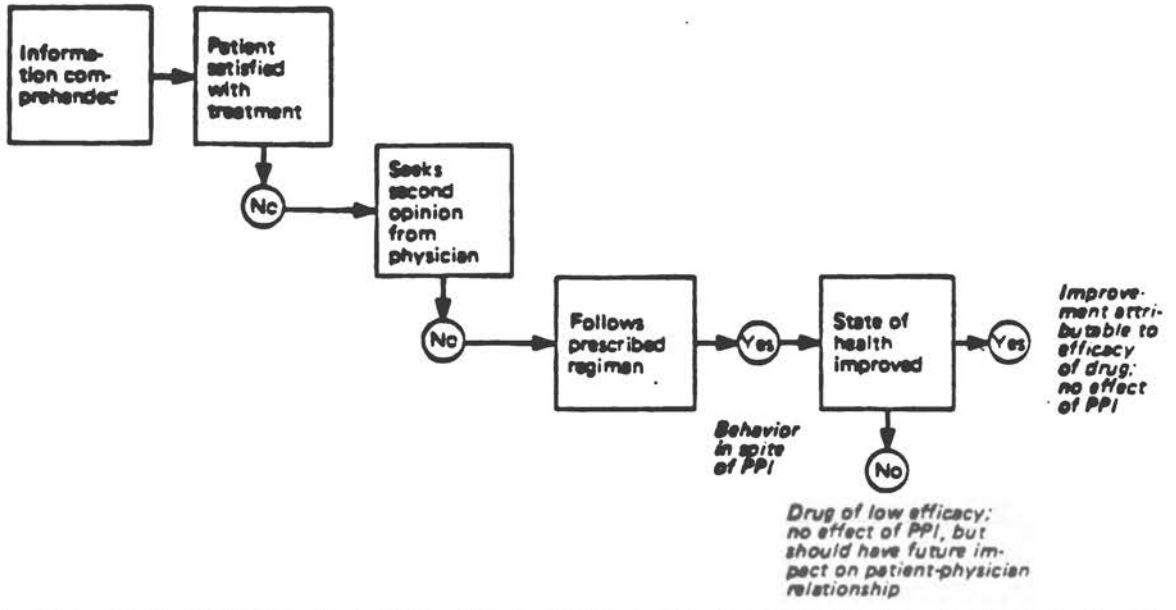
Although each of the purposes mentioned above may be applicable to certain PPIs, none seems equally applicable to all. Thus, care must be taken in the selection of drugs and types of patients to be included in PPI research so that the question of whether PPIs achieve certain benefits receives a fair test. In some instances, for example, it may be reasonable to hypothesize that the information transmitted in the PPI might influence patients to improve their usage of certain drugs that are not always used in a safe and efficacious manner. However, since such problems are not associated with all drugs, and since not all such problems are necessarily amenable to educational efforts, such expectations of PPI effects are not equally plausible with all drugs. To test hypotheses about the influence on PPIs on patients' decisions, compliance, the incidence of adverse reactions, or physicians' prescribing behavior, careful thought must be given to the selection of the drug and the type of patients for whom the drug is prescribed. It is important to learn about circumstances in which effects do and do not occur.

A related point concerns the interpretation of results from studies of the effects of PPIs. The meaning of evidence about PPIs lack of influence on such topics as compliance, patients' involvement in decision-making, or the incidence of adverse reactions must be interpreted in light of the type of patient and drug with which the PPI is used. The reason

FIGURE 1. IDEAL AND ALTERNATIVE MODELS OF PPI EFFECTS ON PATIENTS' HEALTH



3a.


Information comprehended
Patient satisfied with treatment
No
Seeks second opinion from physician
No
Follows prescribed regimen
Yes
State of health improved
Yes
Improvement attributable to efficacy of drug; no effect of PPI
Behavior in spite of PPI
No
Drug of low efficacy; no effect of PPI, but should have future impact on patient-physician relationship

4.

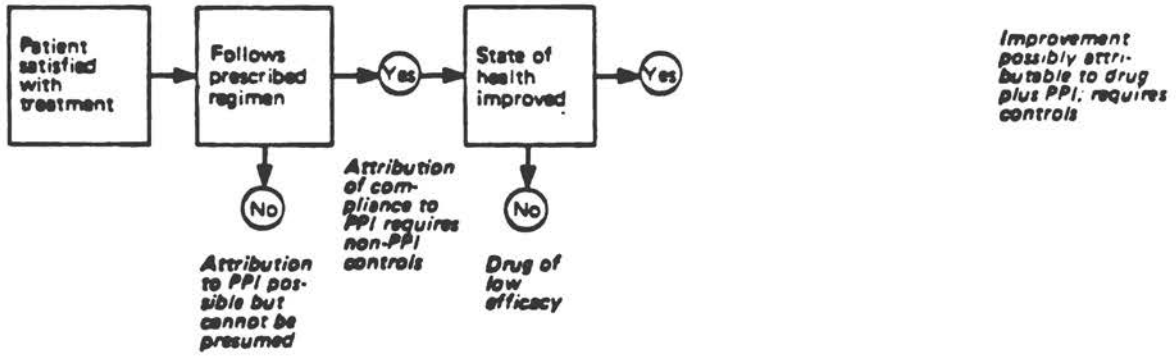
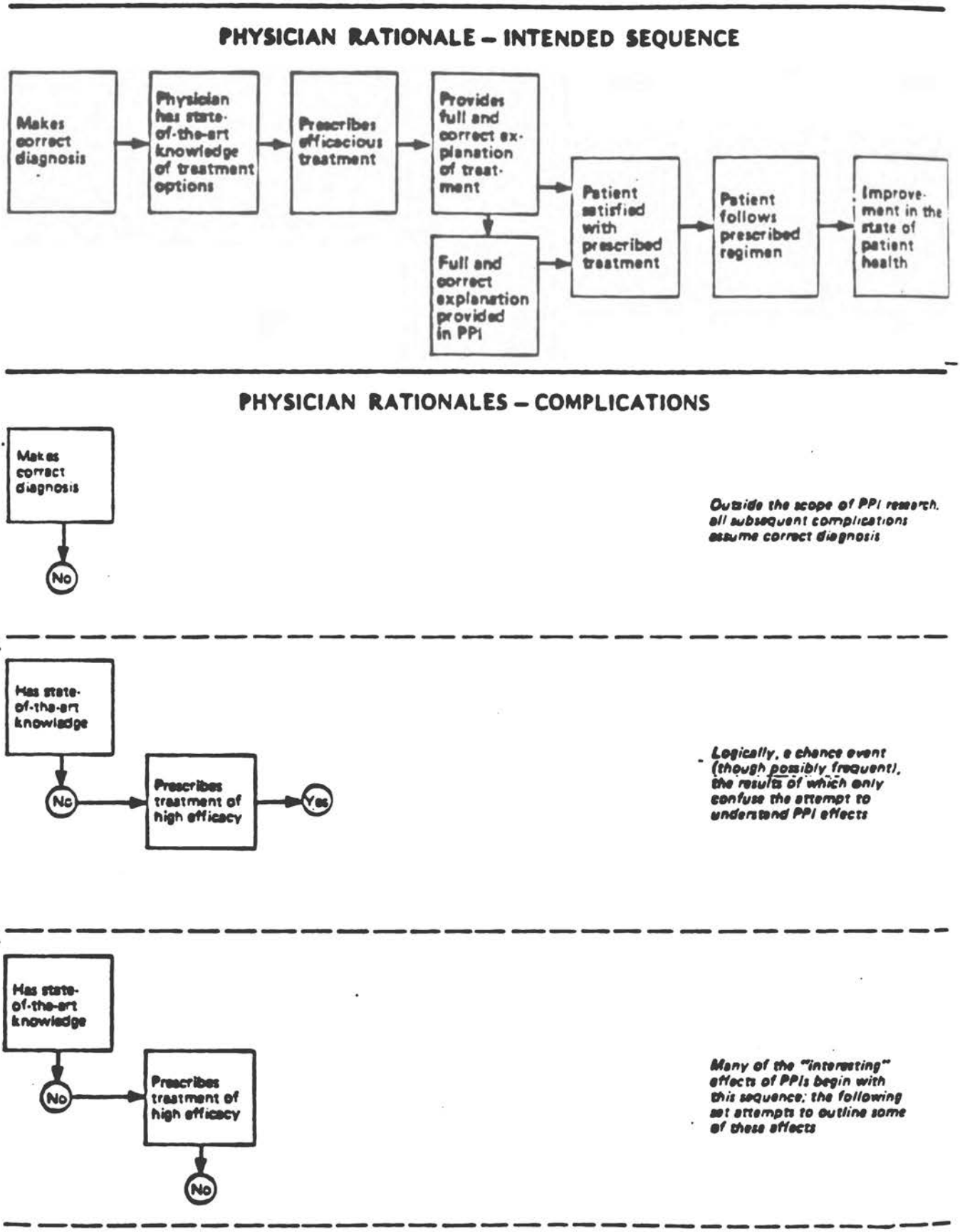
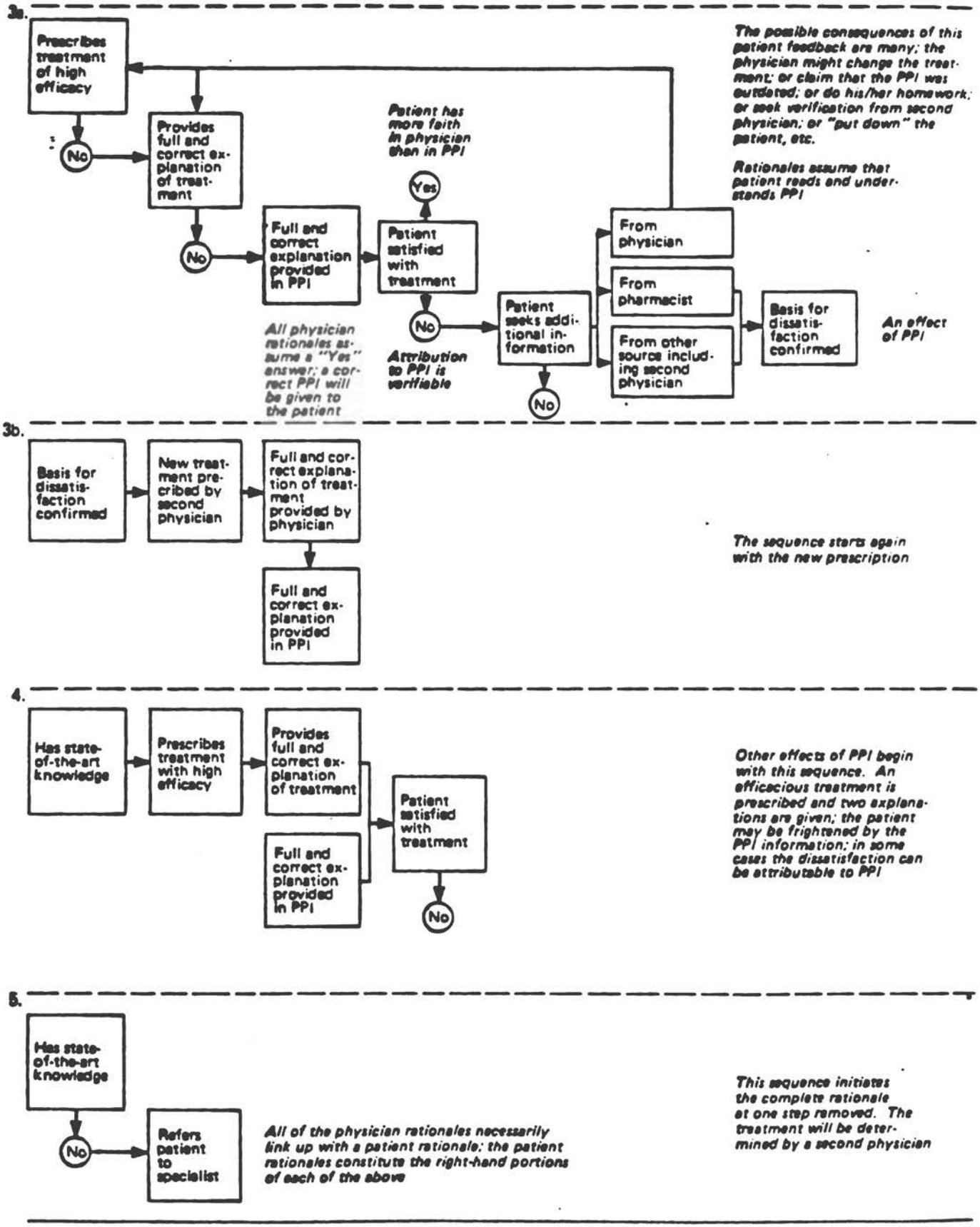

Patient satisfied with treatment
Follows prescribed regimen
Yes
State of health improved
Yes
Improvement possibly attributable to drug plus PPI; requires controls
No
Attribution to PPI possible but cannot be presumed
Attribution of compliance to PPI requires non-PPI controls
No
Drug of low efficacy

FIGURE 2. IDEAL AND ALTERNATIVE MODELS OF PHYSICIAN BEHAVIOR, PPI, AND HEALTH OUTCOMES




3a.
Prescribes treatment of high efficacy
No
Provides full and correct explanation of treatment
No
Full and correct explanation provided in PPI
Patient has more faith in physician than in PPI
Yes
Patient satisfied with treatment
No
Patient seeks additional information
No
From physician
From pharmacist
From other source including second physician
Basis for dissatisfaction confirmed
An effect of PPI
The possible consequences of this patient feedback are many; the physician might change the treatment; or claim that the PPI was outdated; or do his/her homework; or seek verification from second physician; or "put down" the patient, etc.
Rationales assume that patient reads and understands PPI
All physician rationales assume a "Yes" answer; a correct PPI will be given to the patient
Attribution to PPI is verifiable
3b.
Basis for dissatisfaction confirmed
New treatment prescribed by second physician
Full and correct explanation of treatment provided by physician
Full and correct explanation provided in PPI
The sequence starts again with the new prescription
4.
Has state-of-the-art knowledge
Prescribes treatment with high efficacy
Provides full and correct explanation of treatment
Full and correct explanation provided in PPI
Patient satisfied with treatment
No
Other effects of PPI begin with this sequence. An efficacious treatment is prescribed and two explanations are given; the patient may be frightened by the PPI information; in some cases the dissatisfaction can be attributable to PPI
5.
Has state-of-the-art knowledge
No
Refers patient to specialist
All of the physician rationales necessarily link up with a patient rationale; the patient rationales constitute the right-hand portions of each of the above
This sequence initiates the complete rationale at one step removed. The treatment will be determined by a second physician

again is that the potential for certain PPI effects undoubtedly varies from drug to drug and according to the type of patient for whom a drug is prescribed.

One further point should be made about the purpose of PPIs. Although a number of possible purposes of PPIs have been discussed above, these purposes are all derivative from, or logically consequent to, the most basic and central purpose of PPIs: to make information relevant to the use of drugs readily available to patients. Patients' cognitive and emotional responses to PPIs and their attitudes toward and evaluation of PPIs, therefore, are appropriate objects of evaluation with all PPIs. Other types of patient responses (for example, their behavior) may be expected to occur primarily with particular drugs or in selected situations. In that sense they are less general in nature.

Specific and Nonspecific Effects of PPIs

A basic distinction can be drawn between effects that may be produced by specific PPIs and broader effects that may occur if PPIs come into general and widespread use. It is reasonable to hypothesize that certain changes in patients' knowledge or behavior might result from their receiving a PPI for a particular drug. However, many other effects that have been predicted for PPIs would be difficult to link to the impact of any particular PPI. For example, the widespread use of PPIs may influence the development of "unit-of-use"* packaging of prescription drugs, facilitate the development of an increased counseling role for pharmacists or nurses, or cause physical changes to be made in pharmacies to store PPIs or allow for the counseling of patients. Such changes would not be attributable to any particular PPI.

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* This term refers to the distribution by manufacturers of drugs that are already packaged for dispensing to the consumer. At present, prescription drugs are characteristically distributed in bulk and re-packaged at pharmacies for distribution to patients. Unit-of-use packaging, which now characterizes over-the-counter medications, would allow PPIs to be inserted in the package by the manufacturer, thereby relieving the pharmacy of the necessity of storing PPIs and locating the proper one for dispensing with each prescription that is prepared. A shift to unit-of-use packaging by manufacturers might in turn be expected to result in changes in the role of the pharmacist; relieved of most counting and pouring responsibilities, the pharmacist's role might take different directions. In some settings, the time savings may be translated to an increased drug monitoring or patient counseling role for pharmacists; the wider use of PPIs may contribute to this by providing a core of information that the pharmacist would feel free to discuss with the patient. In other settings--particularly those that compete primarily on price--unit-of-use packaging may tend to shrink the pharmacist's role.

This is also true of such predicted effects of PPIs as increased egalitarianism in the doctor-patient relationship as the patients' knowledge increases, changed patient expectations regarding the knowledge that should underlie their use of drugs, changes in the information that physicians routinely provide to patients, and changes in prescribing or referral patterns. Some relevant evidence regarding such changes may result from studies of the effects of specific PPIs, but such research would need to be supplemented by trend studies using appropriate indicators. There are basic differences between potential effects of specific PPIs and emergent effects of PPIs as an aggregate phenomenon. The former problem calls for research strategies based on comparison between groups receiving PPIs and those not receiving PPIs. The latter problem calls for longitudinal research strategies involving, for example, sample surveys and epidemiological studies of drug use. Both types of strategies are needed.

Short-run and Long-run Effects

Some related issues arise from the distinction between short-run and long-run effects of PPIs. Some effects may not occur at all in the short run. For example, physicians may not become aware of PPIs as soon as they are introduced and changes in their attitudes or behavior may be delayed as a result. Other effects may occur while PPIs are still new to patients, but may not persist over time. Patients' use of and response to the first few PPIs they receive may not predict their use of and response to the 25th PPI they receive, and readership and use of PPIs may decline as their novelty wears off. On the other hand, patients may come to view PPIs as containing information that is essential to their safe and effective use of drugs, and readership and use of PPIs could increase over time. The important point here is not to predict these trends, but only to note the possibility that they will develop, a possibility that has obvious implications for evaluation strategy.

Regulation and the Role of Research

Another distinction among the potential effects of PPIs is related to their being required by the FDA and that agency's purposes in evaluating them. The committee recognizes two valid and important reasons for studying the effects of PPIs. The first is to contribute to future policy decisions by showing the extent to which the regulations accomplish their purpose or have negative effects on patients or the doctor-patient relationship. The second is to increase our general understanding of broader matters pertaining to our health care system and governmental regulatory processes.

The evaluative and regulatory purposes of PPI research impose some temporal and topical constraints on the research. FDA plans to reassess its PPI regulations after a period of two or three years and can be expected to be concerned primarily with research that will contribute to that end. Evaluation studies done solely for this purpose would presum-

ably confine attention to effects that might be expected in the relatively short run and that are relevant to the agency's regulatory purposes. However, as has been noted, the committee believes that some effects of PPIs might not necessarily develop in the short run, and some short-run effects may not be persistent. Furthermore, some important potential effects of PPIs may be of little relevance to the regulatory actions of an agency such as FDA. For example, the general use of PPIs may produce adaptations and changes in the roles of nurses or of pharmacists in many settings. While the purpose of PPIs is not to produce such changes, and their occurrence might be largely irrelevant to any forseeable FDA policy decisions regarding PPI requirements, the committee views such changes as an important part of the potential effect of PPIs.

The committee believes that PPIs should be studied not only because of what may be learned that will contribute to future regulatory decisions that are now anticipated, but also because of what we may learn about our system of health care and the behavior of patients, physicians, and others. Useful knowledge may be gained about different ways of organizing or paying for health care—the role and effects of PPIs may vary according to such factors as the ready availability of consultation, the presence of ancillary personnel, and the mode of reimbursement that is used. When combined with the results of other studies—for example, of quality of care—this research may help suggest desirable ways to restructure the health care delivery system. Another broader purpose of studying PPIs is to increase our general understanding of the processes by which governmental regulatory actions have their effects and ramify beyond their original purposes. For example, regulatory actions may set in motion some social and political processes in which different occupational groups may seek to gain, legitimate, or retain control over certain functions. The PPI arena may provide a good opportunity to increase our understanding of such matters.

The committee recognizes the limits of FDA's immediate needs and concerns about PPIs and expects that these limits will probably affect FDA's decisions regarding the primary foci of the research that it supports or conducts on the effects of PPIs. Even so, the committee felt that a broader research agenda should be identified in the hope that the full range of possible impacts of PPIs will come under study. The broader issues may be of interest to other federal agencies or private sponsors, and PPIs may be the object of research carried out under various auspices.

The Need for New Research

Finally, a distinction can be drawn between PPI effects about which considerable empirical research has been or is presently being conducted and effects about which little information is available. Although much research has been conducted on the effects of written information in patient education programs, these studies cannot be used to draw firm conclusions about the effects of PPIs. However, there are a smaller number of studies of actual PPIs that contain information of direct relevance.

As was described in Chapter 2, patients' attitudinal and cognitive responses to PPIs have been studied in surveys of oral contraceptive users, using both national and local samples, and local surveys have also been done of patients' responses to PPIs for estrogens and the Progestasert(R) intrauterine contraceptive system.

There is also a growing body of experimental work with PPIs. Experimental designs have been used, or are presently being used, to study a wide variety of attitudinal, cognitive, behavioral, and medical responses to PPIs. Preliminary findings are now available from a study of a thiazide PPI with hypertensive clinic patients (Kanouse and Morris, unpublished), and two studies are underway which will provide information about the effects of prototype PPIs for an antibiotic (erythromycin), an hypnotic (flurazepam hydrochloride), estrogens, and a mild tranquilizer (diazepam). The first three of these PPIs are being studied by the Rand Corporation under contract with FDA; the latter PPI is being studied by Dr. Seymour Fisher, at the University of Texas Medical Branch at Galveston, with grant support from the National Institutes of Mental Health and FDA. The committee sees no need to duplicate this body of work, but believes that such studies provide a useful model for studies of PPIs with other types of drugs and patients.

In summary, the committee concluded that evaluation strategies must recognize the following:

-- PPIs may or may not be used as intended
— the purpose of PPIs is only one source of goals for evaluation
-- the purpose of PPIs may vary to some extent from drug to drug
— PPIs will undoubtedly have some unplanned effects
-- some effects are a hypothetical result of specific PPIs while other effects are a hypothetical result of PPIs in general
— there may be important differences between short-run and long-run effects of PPIs, and that some effects that occur in the short run may change over time
-- some potential effects of PPIs may be studied with any PPI while other potential effects can best be studied by examining selected PPIs,
— some effects of PPIs may be relevant to future policy decisions by FDA while other effects of PPIs may not.

Finally, the committee recognized that some potential effects of PPIs have been the object of sound empirical research while other effects have not, a factor that must be considered in setting future research priorities.

Research Agenda

A broad range of potential intended and unintended effects of PPIs warrants study. The types of studies that can be used to assess these effects can be grouped into three categories: descriptive studies of the ways in which PPIs are actually distributed and used, experimental studies to test specific hypotheses regarding the effects of PPIs on patients, and

indicator or trend studies of long-term effects of PPIs. As will be noted, the power and interest of descriptive and experimental approaches will be considerably enhanced if a longitudinal element can be brought to these approaches.

Before describing the committee's views on a research agenda for the evaluation of the effects of PPIs, one general concern should be noted. The committee strongly recommends that any research activities conducted or supported by the Food and Drug Administration should be insulated from the agency's enforcement activities. This is particularly important in view of the committee's emphasis, stated below, on the importance of descriptive research on how PPIs are actually distributed and used. The purpose of the research recommended by the committee is to gather information that will further our understanding of various matters pertaining to PPIs and to contribute to future policy decisions. The purpose must not be to identify individuals or organizations who are not following the letter or spirit of FDA regulatory requirements; in fact, careful precautions must be taken to protect and preserve the privacy of individuals and the confidentiality of research data. Above all, research data should not be used to single out individuals for punitive action. The committee recognizes that FDA has clear regulatory responsibilities, which could potentially come into conflict with the agency's research activities. The committee's concern stems from recognition of a potential conflict, not from any knowledge of past difficulties of this sort and not from any belief that FDA has any intention of combining research and enforcement activities.

Descriptive Studies of PPI Use

Basic to the assessment of PPIs is good descriptive information about the way they actually come to be distributed and used. Such descriptive research can provide essential information that cannot be obtained through the controlled, experimental designs that have been used in the best studies now available on the effects of PPIs. Although controlled studies using sound experimental design are powerful tools in the assessment of PPIs, they have important limitations. First, the development of a rigorous experimental approach, including a randomly assigned control group not exposed to the intervention under study (in this case, a PPI), is neither feasible for the assessment of certain possible effects of PPIs, because of the scale that would be required, nor are such methods necessary to the collection of much important and valid information about the impact of PPIs. Second, an essential need is for information about how PPIs are used in natural settings, rather than under controlled conditions. For these reasons, the committee concluded that the conduct of descriptive research in natural settings is of high priority at the present time.

A variety of research methods should be considered to obtain descriptive data about the use of PPIs, including such topics as whether and how patients receive PPIs, how PPIs are used by patients (for example, are PPIs read and retained for future reference?), patients' assessments of

the usefulness of PPIs and the information contained therein, physicians' awareness of and attitudes toward PPIs, and the extent to which the PPI and the information it contains becomes an occasion for communication between practitioners (physicians, nurses, or pharmacists) and patients or their families. Well-focused research conducted by solo researchers could shed light on various of these questions regarding the use of PPIs. However, since the use of PPIs involves medical practice, pharmacy practice, and patients, there is much to be gained through the inclusion of all three elements in descriptive research on PPIs. The impact of PPIs on one part of the system (for example, on the knowledge of patients) may produce secondary effects on other elements; that is the nature of a system. In the committee's view, the most desirable way to meet this need is by focusing on several (four to six) locales (communities or neighborhoods), so that the use of PPIs by persons of various ages (pediatric and geriatric patients are of particular interest) and from different educational and ethnic backgrounds can be studied, the use of PPIs in different types of medical and pharmaceutical practice settings can be included, and the real life complexities of the use of PPIs will become evident. Several data-gathering approaches can be employed including observational and survey methods and studies of records.

Observational studies of doctor-patient communication A useful approach to descriptive research is through direct observation or the use of audio or video recordings. Such methods have been used to study doctor-patient interaction and communication in a number of studies (Peterson et al., 1956; Clute, 1963; Barbee et al., 1967; Davis, 1968; Golden and Johnston, 1970; Korsch and Negrete, 1972; Smith, 1974; Bain, 1976; Svarstad, 1976; Boreham and Gibson, 1978; Stiles et al., 1979). Although a variety of schemes have been used to code and analyze doctor-patient communication, the focus here should be on questions, information, and instructions regarding medications and PPIs. The use of observational methods provides the most direct information about the amount and content of doctor-patient communication. Such methods, however, can be used with only limited numbers of physicians, and the effects of the presence of the observer must be considered in the design, conduct, and interpretation of the research. Survey research methods also can be used to study doctor-patient communication (see, for example, Gayton and Walker, 1974; Gray, 1975; Hulka, et al., 1976), and make it possible to study larger numbers in a relatively cost-efficient way. Because the data come from participants' reports of the doctor-patient encounter, however, the quality of the evidence obtained is more open to question than data obtained through observational methods, and difficulties arise in distinguishing between the physician's failure to disclose and the patient's failure to remember, and in interpreting differences among participants in their accounts of the same encounter. Nevertheless, if the purpose of the research is to make comparisons across time (or across experimental and control groups), these problems may be relatively unimportant, as long as the same biases exist under all conditions being compared.

Physician interviews Survey research methods should be used to obtain information about physicians' communication practices and their responses to PPIs, both in the communities under study and in a sound

national sample. A variety of topics would be of interest. What topics do physicians report discussing with patients when prescribing a few indicator drugs? Are physicians aware that patients receive PPIs with drugs and, if so, how did they obtain this information and do they know which drugs are involved? What adaptations, if any, have been made in their practice as a result of PPIs? Do they perceive PPIs as having affected their prescribing, referral, or delegation behavior, their communication with patients (including amount of time spent with patients), patients' communication with them, and patients' willingness to follow medical advice? What are physicians' attitudes toward PPIs? How aware are they of how PPIs are prepared? What are their views about such general topics as the patient's needs for information and the extent to which patients can and should participate in therapeutic decisions? What changes do they recommend in policy regarding PPIs? In settings in which responsibility for discussing the PPI with patients is delegated (for example, to a nurse), data on the communication process and patients' responses to PPIs should also be collected from that person, if possible. If FDA's forthcoming regulations give physicians discretion over whether patients will receive PPIs, questions should be included about the extent of use of that discretion, the situations in which it is exercised, and the criteria that underlie its use.

Patient surveys Patients (or, for children, parents of patients) who have received prescriptions for drugs for which PPIs are required also should be interviewed to probe such topics as whether they are aware of the PPI, whether they read it, whether they found it useful, what they did with it (for example, did they keep it and refer back to it; if so, under what circumstances), whether it affected their thinking about using the drug, their general level of knowledge about important aspects of the drug, whether the PPI prompted them to seek additional information (if so, from whom), and so forth. Questions also could be included about the extent of, and satisfaction with, information obtained orally from the physician, nurse, or pharmacist, particularly if the interviews are done relatively soon after the prescription has been filled. In addition, useful information could be obtained about patients' views about more general matters such as the information they would generally like to receive about drugs that are prescribed, the extent of their interest in participating in medical decision-making, and the general safety of drugs and how readily they should be used.

Observational studies in pharmacies Observational methods can be used to study both the extent of pharmacist-patient communication and the immediate use or disposition of PPIs. However, with regard to the communication question, simple observational methods involve a number of obvious difficulties (regarding efficiency, reactivity of those being observed, and patients' privacy) that can be avoided through the use of simulated patients to present prescriptions for filling. Such methods, used at different types of pharmacies, by different types of patients, and at different points in time could provide a rich source of information about pharmacist-patient communication and the role of the PPI therein. In other situations, it may also be useful for an observer to be present

with pharmacists to learn about patients' immediate responses to pharmacists' provision of information.

There has been debate about the ethics of researchers assuming the role of a client or customer in order to study the operation of an organization or the behavior of persons acting in their occupational or professional capacity. On one extreme such research techniques are innocuous, as with the activities of a newspaper's restaurant critic. At the other extreme is the anthropologist who faked a terminal illness in order to compare different modes of providing care (Buckingham, 1976) or the law students who assumed the role of mental patients in order to study how patients are treated by staff in mental institutions (Rosenhan, 1973). The committee was not of a single mind regarding the ethics of using simulated patients to fill prescriptions as a way of studying the behavior of pharmacists, although such techniques have been used before, apparently without provoking serious criticism (Campbell and Grisafe, 1975). An important source of ethical reservation in the committee was the possibility that such research could in fact be conducted with the consent of the pharmacist, by seeking permission to do such research unannounced at some unspecified date within the next six months. This raises the question of whether the pharmacists' behavior would be changed. However, social scientists commonly have noted the tendency of behavior to return to normal under such circumstances, even if observers are present. A more serious problem might be raised if significant numbers of pharmacists refused permission, thereby raising questions about selection biases. Nevertheless, the committee felt that the possibility of obtaining consent in the conduct of such research should be investigated.

Pharmacist surveys Another method of collecting useful data would be to interview pharmacists in different types of settings about such matters as adjustments they have made in their pharmacies and their behavior as a result of PPIs, their perceptions of ways in which PPIs may have changed their relationships with patients and with physicians, the extent to which PPIs have prompted questions from patients and the circumstances under which this has occurred, and their evaluation of PPIs and suggestions for changes. If FDA regulations give physicians the option of withholding PPIs from patients, pharmacists should also be asked about the extent to which, and the circumstances under which, this is occurring. Pharmacy records may also be a useful source of information with regard to this question. The patient medication records systems that have been developed in some settings may be quite useful in studying such topics as adverse reactions, refill rates (a potentially useful indicator of PPI effects with certain drugs), and other patterns of drug use. The existence of such records systems should be considered in selecting sites for research on the effects of PPIs.

Timing of descriptive studies The timing of descriptive studies outlined above is of considerable importance. To contribute maximally to the planned reassessment of PPIs, studies should be undertaken after several PPIs (for drugs that are relatively frequently and widely used) have been in use for a sufficiently long period of time that initial adjustments in their distribution and use have been made. These studies, how-

ever, should also be undertaken soon enough for the results to be available for the planned reassessment of PPI policy. The timing must mediate between these points; descriptive studies probably should be conducted no sooner than one year and no later than two years after several new PPIs come into general use. Also, the usefulness of descriptive studies will be heightened if data are collected at several times so that changes can be observed. Longitudinal approaches are discussed later in this report.

Descriptive studies and causal attribution The potential usefulness of the research approaches described above is not limited to matters of pure description. The obtaining of base-line information (in the pre-PPI period) and the study of settings in which PPIs are not in use would greatly contribute to judgments about the effects of PPIs on such matters as communication patterns, patients' attitudes and expectations regarding the information they should receive and the extent to which they should be involved in decisions regarding their own care, patient satisfaction with and trust in the health care they receive, and so forth. Several possibilities for obtaining relevant information should be considered:

- To some extent, studies that have been conducted for other purposes can be used as a base line. Such studies range from observational research on doctor-patient communication (for example, Svarstad, 1976) to surveys of patient expectations and satisfaction. It is possible that some relevant studies are under way at present.

- Some base-line information could be collected in the communities that are to be the focus of the descriptive studies outlined above. An initial survey of physicians could obtain information about existing practices regarding provision of information to patients, referral and delegation behavior, and perceptions of patients' expectations and needs for information about prescription drugs. Similarly, a survey of patients' perceptions and expectations could be done. Finally, useful base-line information could be obtained using simulated patients in pharmacies.

- As is described below, existing records and data may be used for certain comparative purposes, for example, regarding prescribing patterns.

- PPI requirements under FDA regulations will presumably be uniform throughout the U.S. An obvious difficulty in evaluating such a system-wide event is the lack of a comparison group. Questions will inevitably arise whether changes found in before/after studies are due to the event of interest (in this case, PPIs) or to other factors. Thus, the collection of parallel before/after data in situations in which the event of interest (a PPI requirement) does not occur would be of great interest and is, of course, integral to the logic of experimentation. While the committee recommends the conduct of the community-based descriptive studies mentioned above, even in the absence of control communities for comparison purposes, the possibility of developing such control communities should be considered.

- Since FDA's requirements will probably begin with a limited number of drugs, it is conceivable that either pharmaceutical companies or state governments could take actions that would bring PPIs into more extensive use in certain areas (a community or even a state), thereby facilitating comparative studies of the impact of PPIs. Such a proposal, however, raises so many complexities, both political and methodological, that its feasibility seems very questionnable. An alternative that may be more practical would be to conduct control studies in Canada. Although there has been some discussion of establishing PPI requirements in Canada, no plans now exist for instituting such labeling. The health care system of some provinces in Canada is relatively similar to that in the U.S., although differences may exist with regard to doctor-patient relationships, the attitudes of doctors and patients, and regulatory traditions. It may be possible to select several community settings in Canada and to obtain comparable descriptive data for at least two points in time--prior to and after the PPI requirement is implemented in the U.S. While the committee was not able to conduct an extensive investigation of the feasibility of this type of study, or to assure itself completely of the validity of Canadian-American comparisons of this sort, the committee believes that the possibility of conducting some control studies in Canada merits further consideration and investigation. It would be useful to convene a group of investigators from the U.S. and Canada to discuss the validity of the U.S.-Canadian comparison on this topic and the feasibility of some parallel data-collection efforts in the two countries.

Experimental Studies of Patients' Responses

The effect of PPIs on patients' knowledge, attitudes, and behavior is central to the evaluation of PPIs and is the topic that has received the most study to date. Many of the most important potential effects of PPIs can best be studied through an experimental design in which the responses of patients receiving PPIs are compared with those of randomly assigned control patients receiving more general, "placebo" drug information. That basic research design is presently being used in studies that the Rand Corporation is conducting under contract with the FDA, and, in the view of the committee, it is a sound approach to examining hypotheses regarding patients' responses to PPIs.

However, there was some sentiment within the committee in favor of a research design that would also include a group of patients who are given PPIs in the context of a broad program of health education. The context in which patients receive a PPI, and the oral explanation that accompanies it, seem likely to influence both the potential positive and negative effects of PPIs (Green and Faden, 1977). Furthermore, it would be possible to conduct studies in which responses of patients receiving PPIs in the context of a health education program are compared with the responses of patients who are exposed to a health education program that does not include PPIs. Nevertheless, the committee concluded that the highest research priorities should go to studies that examine the effects of PPIs

as they are most likely to be used in actual practice in the forseeable future. Since the FDA regulations will, in effect, require that PPIs be added to the existing flow of information between practitioners and patients, the highest research priority should go to studies to assess the impact of PPIs under these circumstances. It should be noted, however, that the descriptive studies recommended above may provide data on the extent to which PPI information is supplemented by the physician or pharmacist, and the effects of any variations therein can be examined in the analysis of the data. While this is clearly less adequate than an experimental approach to the question, it may nevertheless suggest ways that the use of PPIs can be improved.

Topics to be studied Among the questions that the committee believes can be studied most appropriately through an experimental design strategy are:

- Do patients who receive PPIs become more knowledgeable than other patients about what the drug is for, when it should be taken, when it should be discontinued, necessary precautions, what should be monitored, and so forth? To what extent are patients who receive a PPI confused by the information it contains?

- Do PPIs affect patients' orientation toward their condition and the recommended therapy? Are patients who receive PPIs more anxious than other patients about whether they should use the prescribed drug? Do PPIs affect patients' perceptions about such matters as the likelihood that the drug will benefit or harm them and the consequences of failure to use the drug? Are patients who receive PPIs more or less confident about their prognosis? Do PPIs affect their morale? How are these matters affected by oral communication from health practitioners?

- Are patients who receive PPIs more likely to use the drug in the manner intended? (A variety of "compliance" measures are available. In general, the best methods of measuring compliance are also the most expensive. In the present case, the need for a measure of the "true" level of compliance is less urgent than the need for a measure that will serve the purpose of facilitating comparisons between groups. Thus, the methods selected for measuring compliance should produce a plausible measure of compliance and must operate equally well in the experimental and control groups.)

- Do PPIs affect therapeutic outcome? (Again, many measures of therapeutic outcome might be available, with the best measures probably the most expensive. However, interview questions about patients' perceptions of their own condition, whether they have returned to normal activities, and so forth, would provide some indicators of therapeutic outcome and would be quite useful for comparative purposes.)

- Do PPIs affect the experience or attribution of side effects or

the reporting of side effects to the physician or pharmacist? (Various methods of study are available, including the use of symptom checklists that include some "dummy" items of symptoms not associated with the drug.)

- Do PPIs affect patients' attitudes (trust, confidence) toward their physician?

- Are PPIs associated with changes in the sharing of medications by patients?

- Do PPIs lead to discussions about the medication with health professionals, family members, or friends?

Interviews in the experimental studies should also include questions similar to the basic questions asked in the descriptive studies--whether the patient is aware of receiving the written material (either PPI or "placebo") and what was done with it (was it read, was it kept)—in addition to questions about possible responses to the material.

Need for additional research Past or present research has used experimental designs to study patient responses to PPIs for thiazides (diuretics used chronically by hypertensives), estrogens, an antibiotic (erythromycin), a hypnotic (flurazepam), and a minor tranquilizer (diazepam). These studies will provide a solid body of information about outpatients' responses to PPIs with some commonly used drugs whose use raises many of the issues to which PPIs are relevant, such as compliance, patients' decision-making, incidence of side effects, and patient confusion and anxiety. In light of the existence of this body of research, the committee views the conduct of additional experimental PPI research of lower priority than the descriptive studies described earlier. However, given the widespread concern about the possible negative effects of PPIs on patients, the committee nevertheless believes that there would be considerable merit in conducting additional experimental research on the effects of PPIs.

The committee did not attempt to make recommendations about the specific foci of future experimental studies because some key aspects of FDA's regulatory plans remain speculative. The committee did not know, for example, whether PPIs will be required with drugs administered to hospitalized patients, with cancer chemotherapeutic agents, or with drugs used for psychotherapeutic purposes with severely disturbed patients. The use of PPIs in any of these situations raises some potentially difficult issues that merit careful examination and evaluation. Furthermore, the committee had no knowledge of which drugs will be selected for initial PPIs; since the research design recommended by the committee requires that not all patients receive PPIs, a drug covered by PPI requirements would not be a suitable candidate for an experimental study.

The committee had extensive discussions about variations of potential importance among drugs and among types of patients and conditions for which drugs are used. In the committee's view, it is reasonable to hypothesize

that such variations may be associated with differences in the effects of PPIs on patients. It is important, therefore, that dimensions such as the following be comprehended in studies using an experimental design:

- Drugs used for acute conditions and drugs used on a chronic basis, since compliance studies show that patients' responses to the one type may not be generalizable to the other.

- Drugs that typically produce no effects of which the patient is aware, and drugs that produce subjective effects, because of possible variation in the role that the PPI may play in patients' interpretations of their responses to the drug.

- Drugs with relatively high and low risk, since a major concern regarding PPIs is whether patients will be able to understand and interpret properly discussions of risks and side effects in PPIs.

- Drugs for which there are recognized compliance problems, since proved compliance is frequently offered as a potential benefit of PPIs.

- Drugs for which mistakes in usage may have serious implications, since a reduction in errors is another benefit of PPIs about which hope has been expressed.

- Drugs to which patients may seek access from physicians in order to meet self-defined needs (for example, weight loss, assistance in sleeping, control of anxiety, or relief from pain), since it has been suggested that PPIs may curb patients' demands for drugs by increasing their general awareness of the possibility of side effects and adverse reactions.

Certain other characteristics of drugs may influence their suitability for study in PPI evaluations. It may be useful to include in experimental studies (a) drugs for which evidence of efficacy is questionnable and (b) drugs about which serious concern exists regarding misuse or inappropriate prescribing. These characteristics are relevant to hypotheses about the possible impact of PPIs on physicians' prescribing behavior, and the research discussed in this section pertains to patients' responses to PPIs. However, one path by which the information in PPIs may come to physicians' attention is through questions raised by patients; thus, it may be useful to include in experimental studies PPIs with drugs that are of questionable efficacy or are believed to be frequently prescribed inappropriately. Such research may contribute to our understanding of the nature of, and limits to, the patient's role when drug therapy is involved in medical care.

In addition, as was noted earlier, the committee believes that it is essential to obtain information about the effects of PPIs with different types of patients (age, education, and ethnicity are all of potential importance) and in different types of health care settings.

Many of the dimensions mentioned above have been covered in past experimental studies of PPIs or in studies now under way. The selection of drugs and settings for future studies should be done to maximize both the number of additional dimensions that are studied and the number of settings and types of patients about which information is obtained.

Studies of Long-term Effects of PPIs

In order to assess the broader, long-term effects of PPIs and the stability of initial responses to PPIs, a number of research approaches are warranted.

First, since considerable interest has developed in PPIs' potential effects on physicians' prescribing behavior, data from the National Prescription Audit and the National Disease and Therapeutic Index should be used to study such hypothesized effects as the reduction in the use of drugs that have been thought to be over-prescribed and drugs that have relatively low benefit in relation to their risk, avoidance of drugs that are accompanied by PPIs, and the narrowing of the range and variety of drugs that physicians prescribe. This analysis should be compared to the physician and pharmacist reports of changes in prescribing behavior, to provide a degree of mutual validation. Finally, because similar data are available in Canada, comparisons can be made of trends in a setting in which PPIs are not in use.

Second, replication of certain descriptive studies several years after PPIs have come into general use will greatly enhance their utility. Only through such replication will trends become apparent in such important topics as patients' reading and use of PPIs; patients' general orientation toward their physicians, medical decision-making, and drugs; physicians' communication behavior and perceptions of patients' expectations; physicians' modes of adaptation to PPIs including their prescribing, referral, and delegation behavior; and pharmacists' adaptations to PPIs and their patterns of communication with patients.

Third, PPIs have the potential for producing a number of changes of a sort that are not amenable to survey research, experimental studies, or records studies. These topics include (1) the impact of PPIs on the liability of manufacturers and practitioners, a matter that should also be given careful consideration by FDA in the planning of its PPI program; (2) the extent to which PPIs facilitate the development of more extensive counseling activities among pharmacists and nurses, perhaps prompting political struggles regarding state licensure laws and policy disputes regarding third party reimbursement for these activities; (3) the impact of PPIs on the retail pharmaceutical industry, including the development of unit-of-use packaging and the evolution of the pharmacist's role in different types of settings (for example, independent pharmacies vs. chain pharmacies). Assessment of these effects by scholars in the appropriate disciplines (for example, law, medical sociology, political science, or the sociology of occupations) should be encouraged. Finally, because

cost is of such major concern in health care today, FDA should be prepared to answer questions regarding the costs introduced by PPIs and the cost savings that they may produce. This can be done both by attending to the cost-relevant dimensions of the studies recommended above and by preparing independent estimates of the costs associated with the preparation and distribution of PPIs.

Fourth, where experimental studies of patients' responses to PPIs have produced evidence of either positive or negative effects of PPIs, and where such findings have played an important role in policy decisions regarding PPIs, consideration should be given to the replication of key experimental studies 3 to 5 years after PPIs have come into general commerce to note the extent to which any major beneficial or harmful effects of PPIs are stable over time.

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APPENDIX A

Individuals and Organizations Who Appeared at the Public Meeting or Provided Written Information to the Committee

American College of Nurse Midwives
American Nurses' Association
*Mr. John Bowdish (Burroughs-Wellcome Company)
*Jonathon O. Cole, M.D. (American Psychiatric Association)
James W. Cooper, Jr., Ph.D. (University of Georgia School of Pharmacy)
Donald A. Dee, R.Ph., M.S. (Minnesota State Pharmaceutical Association)
*E. Richard Dorsey, M.D. (Ohio State Medical Association)
Stephen A. Eraker, M.D. (Stanford University Medical Center)
Robert B. Greenberg (American Society of Hospital Pharmacists)
*Ms. Doris Haire (National Women's Health Network)
*William H. Heller, Ph.D. (U.S. Pharmacopeial Convention)
*Ms. Joan Hoover (American Diabetes Association**)
*Paul Kaufman, M.D. (Pharmaceutical Manufacturers Association)
Louis Lasagna, M.D. (University of Rochester School of Medicine and Dentistry)
Joseph L. Melnick, M.D. (Baylor College of Medicine)
*George Monahan, M.D. (Warner-Lambert Company)
*James Moss, M.D. (American Society of Internal Medicine)
*Richard P. Penna, Pharm.D. (American Pharmaceutical Association)
*Wayne L. Russell, Pharm.D. (St. Louis College of Pharmacy)
*George M. Ryan, Jr., M.D. (American College of Obstetricians and Gynecologists)
Monroe E. Trout, M.D.
S. O. Waife, M.D. (Eli Lilly and Company)
*Philip D. Walson, M.D. (University of Arizona Health Sciences Center)
*Ms. Phyllis S. Wetherill (DES Registry**)

*Presented statement orally at Public Meeting, February 13, 1979.
**Speaker's views not presented on behalf of organization.