Package Inserts for Prescription Drugs as Evidence in Medical Malpractice Suits

The Food and Drug Administration (FDA) requires drug manufacturers to accompany shipments of prescription drugs with "package inserts" that describe the drug, summarize its possible beneficial and harmful effects on the patient, and give the doctor directions for its use.¹ The insert is directed to the prescribing physician and is not seen by the patient.² The information on the insert is potentially important evidence in trials to determine who should

¹ The legal provisions that govern package inserts for prescription drugs are found in a somewhat confused mixture of statutes and regulations. Section 502(f) of the Federal Food, Drug, and Cosmetics Act provides that a drug is "misbranded" if its labeling does not contain "adequate directions for use" and adequate warnings against possible hazards, but a proviso allows the Secretary to exempt certain drugs from the "directions for use" requirement if he determines that such information is "not necessary for the protection of the public health." 21 U.S.C. § 352(f) (1970). Section 503(b) of the Act defines which drugs require prescriptions and exempts drugs dispensed by prescription from the requirements of section 502(f) if the labeling contains, among other things, the directions for use and any cautionary statements contained in the doctor's prescription. 21 U.S.C. § 353(b) (1970). The FDA takes the position that "prescription drugs" are still subject to the requirements of section 502(f) until they are "dispensed by prescription," and the agency has used the § 502(f) proviso as a basis for promulgating regulations on prescription drug labeling. 21 C.F.R. § 201.100(c) (1976). This rather awkward use of authority exempts a drug from the "directions for use" requirement if its labeling contains not only directions for use, but the more extensive information required by the FDA's regulations. See 21 C.F.R. § 201.100 (1976).

² Although doctors usually do not see the inserts mailed with drug shipments, the insert information for most drugs is printed at the manufacturer's expense in the Physician's Desk Reference (PDR), which is published annually and supplemented quarterly by Medical Economics. The PDR is distributed free of charge to all licensed physicians.

The package dispensed by prescription to the patient is exempted from the labeling requirements of § 502(f) by § 503(b)(2). 21 U.S.C. § 353(b)(2) (1970). Nevertheless, the FDA has recently proposed and issued regulations requiring package inserts directed to patients. E.g., 21 C.F.R. § 310.501-.501a (1976) (patient package information for oral and injectable contraceptives); 40 Fed. Reg. 15,392, 15,397 (1975) (proposing 21 C.F.R. § 1.112(c)(6)(ii), which would require information for the patient to be listed on the package insert for physicians as a precaution). The FDA has defended patient package inserts by arguing that the provisions of § 505 of the Act, giving the agency authority to ensure that drugs are safe and that labeling is not "misleading," overcome the provision that exempts drugs dispensed by prescription from the labeling requirements of § 502(f). The Commissioner asserts that requiring printed patient information does not conflict with the purpose of the § 503(b)(2) exemption, i.e., to avoid self-diagnosis and self-treatment, since the patients must have a prescription to get the drugs in the first place. 40 Fed. Reg. 15,394 (1975). See generally Barrows, Prescription Drug Labeling for Patients, 30 FOOD, DRUG & COSM. L.J. 50 (1975); Goldstein, Drug Package Inserts for Patients, TRAL, Feb. 1977, at 55; Joubert & Lasagna, Patient Package Inserts (pts. 1 & 2), 18 CLIN. PHARM. & THERAPEUTICS 507, 663 (1975); Rheingold, Products Liability: The Ethical Drug Manufacturer's Liability, 18 Rutgers L. Rev. 947, 985-87 (1964).
bear the loss when the use of a prescription drug has allegedly injured a patient. Inserts are accepted as critical evidence of whether a drug manufacturer has fulfilled its duty to warn the prescribers and users of its potentially hazardous product. This comment investigates the more controversial role of package inserts as evidence in a malpractice suit against the prescribing doctor.

The recent developments in medical malpractice litigation make an analysis of the proper role of package inserts particularly timely. Courts have traditionally measured the standard of care in medical malpractice trials by the customary practice of physicians in the defendant's community and have required that the standard of care and causation be proved by expert testimony. However, growing doubts over the justification for these special rules and concern over the difficulty plaintiffs have experienced in acquiring expert testimony—a phenomenon blamed by some on a "conspiracy of silence" among doctors unwilling to testify against each other—have led to an erosion of the preferred status of medical defendants. In suits involving prescription drugs, package inserts offer plaintiffs and courts an attractive alternative to the traditional professional standard of care rule and expert testimony requirement. Inserts are related to aspects of the prescription decision that appear more amenable to objective resolution than other medical

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4 See text and note at note 164 infra.


judgments; a drug manufacturer may be better informed of the qualities of its product than most doctors; and the federal government's participation in the preparation of inserts lends them an aura of authority. Several courts have responded to these characteristics and, with support from commentators, have granted inserts special status as evidence in cases involving the alleged misuse of prescription drugs. However, neither the courts nor the commentators have adequately identified and analyzed the questions raised by the use of inserts as evidence.

This comment attempts to fill the analytical gaps in the case discussions by examining the inserts, articulating the arguments for and against their use as evidence, and suggesting how courts can use inserts to minimize the conflicts between safeguarding the prescribing doctor's informed, independent judgment and protecting the patient's right to nonnegligent treatment.

I. THE JUDICIAL TREATMENT OF INSERT EVIDENCE

The plaintiff in a malpractice suit must prove that the doctor owed him a duty to exercise a standard of care which the doctor failed to meet, and that this failure caused him the damages he seeks to recover. Inserts have usually been introduced by plaintiffs to prove the proper standard of care owed by the defendant doctor, but the insert information is also relevant to the plaintiff's proof of causation, and could be used defensively by doctors on both the standard of care and causation issues.

The cases that consider how to treat package inserts in suits against prescribing doctors reveal a variety of approaches. Some courts have avoided deciding how to treat insert evidence by finding that a proper foundation for admission had not been laid, or that

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See text and notes at notes 176-79 infra.
9 See, e.g., Haven v. Randolph, 342 F. Supp. 538 (D.D.C. 1972) (insert most relied on by plaintiff not in effect when the drug was used); Stottlemire v. Cawood, 213 F. Supp. 897 (D.D.C. 1963) (insert information introduced in the form of manufacturer's answer to an interrogatory, without copies or proof of circulation, was inadmissible against defendant doctor); Meier v. Ross Gen. Hosp., 67 Cal. Rptr. 471, 474 (Dist. Ct. App.) (no proper foundation laid, no offer of proof made when objection sustained), rev'd on other grounds, 69 Cal. 2d 420, 446 P.2d 519, 71 Cal. Rptr. 903 (1968); Allen v. Leonard, 270 Cal. App. 2d 209, 75 Cal. Rptr. 840 (Dist. Ct. App. 1969) (pamphlet in evidence printed and circulated after prescription). If the insert is introduced on the issue of causation, it will be relevant even if published after the treatment in question.
the exclusion or admission of the insert had not been prejudicial.\textsuperscript{11} A number of courts have recognized that inserts, like medical treatises, are hearsay evidence if used to prove the truth of the statements they contain.\textsuperscript{12} Some of these courts have avoided the hearsay objection by admitting the inserts to prove something other than the truth of the statements they contain.\textsuperscript{13} Other courts have held inserts admissible as evidence of the standard of care without explicitly mentioning the hearsay rule. These decisions have focused on the proper weight to assign inserts in light of the policies governing the rules of liability and evidence in malpractice suits.\textsuperscript{14}

The earlier cases allowing plaintiffs to introduce insert evidence exhibit caution and reluctance in departing from the traditional rule that the standard of care is determined by expert testimony defining the customary practice of the professional community involved. In \textit{Salgo v. Leland Stanford Jr. University Board of Trustees},\textsuperscript{15} for example, the plaintiff introduced insert information on the proper dosage of a drug that had allegedly been administered to him in excessive amounts. The court held that the insert was admissible, but for a limited purpose: it "cannot establish as a matter of law the standard of care required of a physician in the use of a drug."\textsuperscript{16}

Later cases have expanded the role of inserts as evidence of the standard of care, but these cases have sometimes involved extreme facts.\textsuperscript{17} Several of the decisions expanding the role of inserts as evidence have involved the drug Chloromycetin (chloramphenicol). This drug, an antibiotic effective against a wide range of bacteria,

\textsuperscript{11} E.g., Marsh v. Arnold, 446 S.W.2d 949, 953 (Tex. Civ. App. 1969) (exclusion of insert from evidence held nonprejudicial where insert had been used extensively in cross-examination).


\textsuperscript{13} See, e.g., Sanzari v. Rosenfeld, 34 N.J. 128, 167 A.2d 625 (1961); Koury v. Follo 272 N.C. 366, 158 S.E.2d 548 (1968); text and notes at notes 105-11 infra.


\textsuperscript{16} Id. at 557, 317 P.2d at 180. Defendant and amicus briefs had warned that inserts were conservative and quickly outdated, and that medical progress could be significantly impaired "if physicians were required to follow blindly the suggestions of the manufacturers who prepare but do not use [drugs]." \textit{Id.}

\textsuperscript{17} See, e.g., Incollingo v. Ewing, 444 Pa. 263, 282 A.2d 206 (1971) (mother administered Chloromycetin to her child without a doctor's supervision after lying to a doctor to obtain a renewal of the prescription; insert information warning against "indiscriminate use" of the drug, together with independent medical testimony, overcame a defense based on the custom of the profession).
became quite popular among doctors after extensive promotion by the manufacturer. The drug’s broad effectiveness made it appear an attractive remedy for many minor infections since a doctor could often assume that it would work without having to identify the particular bacteria involved. However, clinical experience with the drug revealed that it induced fatal aplastic anemia in a small percentage of recipients.

*Mulder v. Parke Davis & Co.*, currently the leading decision on insert evidence in medical malpractice trials, involved a patient who had died of aplastic anemia after receiving Chloromycetin for an ear infection. The insert warnings clearly linked the drug with fatal cases of aplastic anemia and recommended that its use be restricted to serious illnesses where other drugs were ineffective. Adequate blood studies during treatment were termed “essential.”

The plaintiff alleged that the doctor had been negligent in prescribing such a dangerous drug, in prescribing a dose too low to cure the infection and prolonging treatment, and in failing to perform adequate blood tests. The Minnesota Supreme Court began its opinion by criticizing the medical profession for making it difficult for plaintiffs to secure qualified expert testimony in malpractice actions. The plaintiff had called three experts, but none was currently practicing in the community, and the trial court had stricken much of their testimony. One expert had testified that the proper practice for a doctor not familiar with a drug was to follow the manufacturer’s advice. The high court, reversing the trial court’s ruling, held that this testimony was “perfectly competent” and noted that “the manufacturer does have a far better opportunity than the ordinary practitioner to know and understand how and when its own product should be used.”

The supreme court upset a directed verdict for the defendant, finding the evidence on the professional standard of care “not strong,” but “adequate to make a prima facie case. Where the dosage is prescribed by the manufacturer, testimony of the physician’s failure to adhere to its recommendation is sufficient evi-

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20 *Id.* at 334-35, 181 N.W.2d at 884-85. For a copy of the Chloromycetin insert, revised as of 1968 and obtained from a pharmacy shelf in June, 1977, see Appendix infra.
21 The defendant had found that Chloromycetin was the most effective of fifteen drugs he tested on the bacteria responsible for the infection, and prescribed a dosage lower than that recommended in the insert. The doctor performed a blood test once in the six months during which the patient received five four-day prescriptions of the drug. *Id.* at 333-34, 181 N.W.2d 884.
22 *Id.* at 338, 181 N.W.2d at 887.
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... evidence to require him to explain the reason for his deviation.”

In response to an amicus petition for rehearing and clarification filed by the state medical association, the court summarized the rules it intended to follow in the future:

Where a drug manufacturer recommends to the medical profession (1) the conditions under which its drug should be prescribed; (2) the disorders it is designed to relieve; (3) the precautionary measures which should be observed; and (4) warns of the dangers which are inherent in its use, a doctor’s deviation from such recommendations is prima facie evidence of negligence if there is competent medical testimony that his patient’s injury or death resulted from the doctor’s failure to adhere to the recommendations.

Under such circumstances, it is incumbent on the doctor to disclose his reasons for departing from the procedures recommended by the manufacturer. Although it will ordinarily be a jury question whether the doctor has justified or excused his deviation, there may be situations where as a matter of law the explanation exonerates him unless rebutted by other competent medical testimony.

The pattern of reasoning in Mulder resembles that in earlier cases broadening the admissibility of inserts: concern about the inequities resulting from the expert testimony requirement leads to an attempt to aid plaintiffs by giving more weight to the package insert. Mulder advances the prior case law in several respects. The court’s rules attempt to define what aspects of insert information are relevant to the proper standard of care and to clarify the weight to be given insert evidence and the possibility of rebutting such evidence. The opinion is conclusory, however, and raises as many questions as it answers. The court does not adequately discuss why inserts should be given this special status. The four things inserts must “do” to qualify are ambiguous, and the reasons for the particular requirements are not explained. A doctor may defend his departure from the insert, but the opinion offers neither examples of such

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23 Id. at 339, 181 N.W.2d at 887.
24 Id. at 339-40, 181 N.W.2d at 887-88.
25 See, e.g., Julien v. Barker, 75 Idaho 413, 418-19, 272 P.2d 718, 721 (1954) (court admitting an insert as “prima facie proof of a proper method of use” of a drug notes allegations that two of plaintiff’s expert witnesses had withdrawn their willingness to testify under pressure from a medical society); Sanzari v. Rosenfeld, 34 N.J. 128, 134-38, 167 A.2d 625, 628-32 (1961) (court allowed insert to prove knowledge of the dangers associated with the drug, noting that the plaintiff had been unable to obtain qualified experts from the community).
a defense nor a rationale for evaluating asserted defenses. Inserts are treated as prima facie evidence of the standard of care, but the court requires independent expert testimony on the causation issue without explaining the basis for this distinction.

Although Mulder has been hailed as the wave of the future, only two jurisdictions have followed the case. Indeed, a recent case from the Minnesota Supreme Court suggests that Mulder is being reexamined. In *Lhotka v. Larson*, a closely divided court affirmed the refusal of a trial judge to give a Mulder instruction. The defendant doctor had prescribed small doses of Seconal, Demerol, and Phenergan for a woman in labor. The woman's child, born prematurely, was given a low chance of survival at birth, suffered a number of cyanotic episodes, and was diagnosed as severely mentally retarded and physically handicapped. The plaintiff claimed that Seconal was contraindicated in cases of premature labor and that the doses of Demerol and Phenergan were excessive. In the absence of a Mulder instruction, the jury found for the defendant. The supreme court affirmed on the ground that the doctor had not clearly departed from any unambiguous manufacturer's instructions. Although injections of Seconal were contraindicated under the circumstances, the drug had been administered orally, and the recommendations on oral administration contained no such contraindication. To support its affirmance, the court emphasized that the plaintiff had been able to secure adequate expert testimony, and that since there were at least six possible causes of the child's condition, the "facts of the case suggest quite strongly that the jury verdict would have been no different even if a Mulder instruction

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27 In Ohligschager v. Proctor Community Hosp., 55 Ill. 2d 411, 303 N.E.2d 392 (1973), the Illinois Supreme Court followed Mulder to hold that insert instructions for the proper administration of a drug and warnings of its potential hazards were sufficient to take the negligence issue to the jury. The court did not adopt the Mulder rule requiring expert testimony to prove causation. However, the opinion notes that the plaintiff had provided expert testimony that the defendant's actions were one possible cause of the injury.

In Mueller v. Mueller, 221 N.W.2d 39 (S.D. 1974), the South Dakota Supreme Court gave a strong endorsement to the Mulder approach:

['T']hese manufacturers' recommendations on the use of drugs are not only admissible but essential in determining the possible lack of care of a doctor where the issue involved is injury from the administration of a drug. We see no reason for the courts to hesitate to use a standard so widely and favorably used in the medical profession.

*Id.* at 43.

28 238 N.W.2d 870 (Minn. 1976).

29 *Id.* at 875 n.17.
had been given." The full significance of Lhotka's limitation on a plaintiff's use of insert evidence is unclear, but the tone of the opinion contrasts sharply with that of Mulder and its progeny.

The cases reveal that the courts have not adequately analyzed the use of inserts in medical malpractice trials. A few opinions have relied on assumptions about the quality of inserts and the use doctors make of them, but no opinion examines the actual process by which particular information is placed on the insert, or even refers to the statutes or regulations governing the preparation of inserts. Such an examination is necessary to assess the reliability of insert evidence and the arguments for and against its use.

II. THE INSERTS

The admissibility and proper role of inserts in medical malpractice trials turn in part on an evaluation of the reliability of inserts as guides for doctors. That reliability is determined by the process that produces inserts and is reflected in the role they play in medical practice.

A. The Insert Preparation Process

Congress designed the regulatory structure that governs package inserts to correct perceived deficiencies and abuses in the production and marketing of drugs. The 1938 Federal Food, Drug and Cosmetics Act and the 1962 amendments to that Act were passed after well-publicized tragedies involving Sulfanilomide and Thalidomide in an effort to prevent future calamities by improving the

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30 Id. at 875.
31 See id. at 877-78 (Chanak, J., dissenting).
32 E.g., Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 317 P.2d 170 (Dist. Ct. App. 1957) (inserts are not current, are overcautious, and are viewed by doctors as merely supplemental to their clinical experience in prescribing the drug); Julien v. Barker, 75 Idaho 413, 272 P.2d 718 (1954) (inserts are reliable because they are prepared by manufacturers with an incentive to be accurate to avoid liability for failure to warn); Mueller v. Mueller, 221 N.W.2d 39 (S.D. 1974) (inserts are "essential" evidence because of rapid technological advances in drugs, the testing requirements imposed on manufacturers and their potential liability, and the practical necessity for doctors to rely on inserts in prescribing).
manufacturing, testing, and labeling of drugs. \textsuperscript{37} The premise of this legislation is that a federal agency is necessary to protect consumers from the products of a profit-seeking drug industry anxious to increase its sales. This premise, which has recently come under severe attack, \textsuperscript{38} together with the relative difficulty of obtaining controlled experimental data on the adverse effects of drugs, explains the general “negative” or cautious bias of FDA regulations and practices. Manufacturers bear the initiative in developing new drugs or new uses for old drugs, and introducing a new drug or changing an insert in a way that will increase sales is much more difficult than withdrawing a drug or changing an insert in a way that will decrease sales.

Since a 1906 prohibition against drug labeling that was “false or misleading in any particular,” \textsuperscript{39} inserts have become increasingly sophisticated, and the government’s role in preparing them has constantly expanded. The history of package inserts \textsuperscript{40} reflects trends


\textsuperscript{38} The continuing trend toward government control of the development and use of prescription medicines has stimulated interest in criticisms of the basic assumptions underlying the regulatory structure. Studies of the effects of the 1962 amendments question the fundamental proposition that increasing the power of an institutionally and politically cautious agency has improved the public welfare. Critics of the amendments point out the reduced rate of innovation since 1962 and assert that the interests of those patients who are harmed by delay and by the absence of new breakthroughs are inadequately represented in the present scheme. See generally Drug Development and Marketing (ed. R. Helms 1975); Regulating New Drugs (ed. R. Landau 1973); W. Wardell & L. Lasagna, Regulation and Drug Development (1975).

These issues have recently been highlighted by controversies over the approval of drugs used widely outside the United States to treat heart disease and cancer. See Legalizing Laetril, NEWSWEEK, May 3, 1977, at 74; Wall St. J., March 7, 1977, at 1, col. 1. Court decisions allowing Laetril, a drug the FDA has refused to approve, to be imported for the treatment of cancer and state legislation designed to achieve the same purpose present a serious challenge to the basic premises of the federal drug laws. See, e.g., Rutherford v. United States, 542 F.2d 1137 (10th Cir. 1976); 42 Fed. Reg. 10,066 (1977).

\textsuperscript{39} Act of June 30, 1906, ch. 3915, 34 Stat. 768. Section 7, defining the term adulterated, and § 8, defining the term misbranded, were the most relevant to labeling. Section 8 was amended to provide specifically that drugs bearing labels with false or misleading statements about therapeutic or curative effects would be deemed misbranded. Act of August 23, 1912, ch. 352, 37 Stat. 416. For regulations on labeling issued under the 1906 Act, see C. DUNN, FEDERAL FOOD, DRUG, AND COSMETIC ACT: A STATEMENT OF ITS LEGISLATIVE RECORD 1348-54 (1938).

\textsuperscript{40} The history of drug labeling statutes and regulations since the 1938 Act can be traced as follows: labeling regulations pursuant to the proviso of § 502(f) were issued in 1938. 3 Fed. Reg. 3168 (1938) (codified at 21 C.F.R. § 2.106(b)(2) (Supp. 1938)). Revised regulations were promulgated in 1944. 9 Fed. Reg. 12,255 (1944) (codified at 21 C.F.R. § 2.106(b) (1946)). In 1951 the Act was amended to define “prescription drug” more specifically and to exempt drugs “dispensed by prescription” from the labeling requirements. Act of Oct. 26, 1951, ch.
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and of the support necessary for each category,\textsuperscript{41} higher requirements for support for certain categories of information,\textsuperscript{42} more extensive records and reports related to insert information,\textsuperscript{43} that uniform format for all inserts and of information required on inserts for similar or identical drugs,\textsuperscript{44} an increased use of expert advice from authorities outside the agency,\textsuperscript{45} and an elimination of exceptions to the insert requirements coupled with an expansion of full FDA authority over almost all prescription drugs.\textsuperscript{46} These trends are reflected in both present agency practices and proposed reforms.

Present FDA regulations require that labeling on or within the package of a prescription drug contain adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is advertised or represented.\textsuperscript{47}

Another labeling regulation, designed to make inserts more orderly and uniform, sets out ten mandatory and three optional categories of information.\textsuperscript{48}

The original insert for a new drug\textsuperscript{49} is approved as part of the


\textsuperscript{44} See, e.g., authorities cited in note 2 supra; 37 Fed. Reg. 23,187 (1972) (codified at 21 C.F.R. § 130.40 (1973)) (current version at 21 C.F.R. § 310.6 (1976)).

\textsuperscript{45} See generally Use of Advisory Committees by the Food and Drug Administration, Hearings Before a Subcomm. of the House Comm. on Government Operations, 93d Cong., 2d Sess. (1974).

\textsuperscript{46} For example, the FDA’s broad interpretation of what drugs are subject to regulation as “new drugs” was upheld by the Supreme Court in 1973. Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640 (1973); Weinberger v. Hynson, Wescott & Dunning, Inc., 412 U.S. 609, 623-27 (1973); see note 49 infra.

\textsuperscript{47} 21 C.F.R. § 201.100(c)(1) (1976).

\textsuperscript{48} 21 C.F.R. § 201.56 (1976). The mandatory headings are: description, actions, indications, contraindications, warnings, precautions, adverse reactions, dosage and administration, overdosage (where applicable), and how supplied. The optional ones are: animal pharmacology and toxicology, clinical studies, and references. A sample insert is printed in the Appendix.

\textsuperscript{49} The 1938 Act defined two categories of “new drug”:
New Drug Application (NDA) submitted by the manufacturer to the FDA. The NDA and the proposed insert are based on tests the drug company develops and administers according to criteria in the statute and regulations. The statute sets out two different testing requirements. The safety of the drug must be shown by "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except . . . [drugs subject to the 1906 Act whose labeling contained the same representations regarding conditions for use];" while efficacy must be proved by "substantial evidence that the drug will have the effect it purports or is represented to have under the condi-

(1) "any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except . . . [drugs subject to the 1906 Act whose labeling contained the same representations regarding conditions for use];" (2) "any drug which has become recognized as required under [(1)] but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."


The regulations defining "new drug" have remained constant since 1939. Regulations first defined four sources of "newness": newness for drug use of a (1) substance or (2) combination of substances or (3) proportion of substances in combination, or (4) "newness of the dosage, or methods, or duration of administration or application, or other conditions of use of the drug prescribed, recommended, or suggested in the labeling thereof" even though the drug is not new when used differently. 3 Fed. Reg. 1847 (1938) (codified at 21 C.F.R. §§ 2.108(1), (2), (3), (4) (1938 Supp.)) (current version at 21 C.F.R. §§ 310.3(h)(1), (2), (3), (5) (1976)). Five months later, another category of "newness" was added: "the newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 3 Fed. Reg. 3161 (1938) (codified at 21 C.F.R. § 2.108(5) (1938 Supp.)) (current version at 21 C.F.R. § 310.3(b)(4) (1976)). It is interesting that this section says nothing specifically about the labeling of the drug.

A series of Supreme Court decisions in 1973 established the agency's authority to determine whether a drug is "new" and affirmed the agency's position that expert opinion used to claim a drug is no longer "new" must be based on the same type of well-controlled studies required to initially prove effectiveness in an NDA. See note 46 supra. The most recent FDA approach to drawing the line between "new" and "old" drugs is based on a drug product's compliance with the composition, manufacturing, and labeling requirements set forth in a "monograph" on the generic product. See notes 72-73 infra.

tions of use prescribed, recommended, or suggested in the proposed labeling."

The statute defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ." FDA regulations elaborate on the data that should be reported in safety and efficacy studies and define the "principles . . . developed over a period of years and . . . recognized by the scientific community as essentials of adequate and well-controlled clinical investigations." The required tests are usually very costly and can significantly delay the introduction of a new drug.

Once the tests are completed and the NDA has been submitted, the drug company and the FDA work out the language of the labeling in negotiations. The manufacturer's position in these negotiations is often based on recommendations from several departments, such as marketing, medical, legal, and regulatory affairs, that have competing interests. Nevertheless, the drug company is usually assumed to favor the widest possible indications and the fewest restrictions on the insert. The FDA side of the negotiations may

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43 E.g., 21 C.F.R. § 314.1(c) (1976) (especially items 10 and 12 of the NDA).
44 21 C.F.R. § 314.111(a)(5)(ii) (1976). These essential principles include: a clear statement of the objectives of the study; methods of selecting and assigning subjects to test groups that will insure suitability, minimize bias, and protect comparability by eliminating extraneous variables; an explanation of the methods of observing and recording results; provision of a "control" (e.g., no treatment, placebo, active treatment, or historical) that can be quantitatively compared with the test results; and a summary of the methods of analysis and evaluation of the data, including any appropriate statistical methods. Id.
45 Approval of a new drug involves several distinct stages or "phases," including preclinical studies in animals, clinical studies in normal humans to test safety, controlled clinical studies to determine effectiveness, and long-term clinical "trials." See AMERICAN ENTERPRISE INSTITUTE, NEW DRUGS: PENDING LEGISLATION 8-10 (1976); Goldberg & Azarnoff, New Drug Investigations in Man: Continuing Unresolved Problems in REGULATING NEW DRUGS 61 (R. Landau ed. 1973).
46 Telephone interview with Ms. Karen Church, Regulatory Affairs Dep't, Abbott Laboratories, in Chicago (Jan. 20, 1976) [hereinafter cited as Church Interview]; telephone interview with Mr. Jerry Head, Regulatory Affairs Dep't, G.D. Searle & Co., in Chicago (Jan. 20, 1976) [hereinafter cited as Head Interview]. The trend toward "class labeling" and "drug monographs" has reduced the significance of negotiations between the FDA and individual manufacturers, and industry spokespeople claimed that more often than not the FDA, rather than the manufacturer, writes the inserts. Telephone interview with Ms. Diane French, Medical Dep't, Abbott Laboratories, in Chicago (Jan. 1976) [hereinafter cited as French Interview]; Head Interview supra; see text and notes at notes 72-73 infra.
47 French Interview, supra note 56; Head Interview, supra note 56.
48 This assumption is based on the manufacturer's incentive to expand sales. Interviews with industry personnel indicate that this assumption is too simplistic. The insert is viewed as the "manufacturer's number one defense" in court when a doctor has used a drug for a
involve a number of persons, including medical officers and outside experts in the relevant field. The agency normally takes a cautious approach, shaped by the structure of its regulations and a sensitivity to congressional investigations. If the company disagrees with the agency's conclusions, it has a right to a hearing before an administrative law judge and can appeal the result to a court of appeals.

After an NDA is approved, data-gathering and reporting requirements come into play. The manufacturer and the FDA must
assemble both positive and negative information on the drug, but the emphasis in the regulations, as in the statute,\(^6\) is on collecting negative information\(^4\) that will "facilitate a determination whether there may be grounds . . . to suspend or withdraw approval of the application."\(^5\) The FDA will withdraw approval if new information indicates that the drug is not safe and effective for use under the conditions mentioned in the insert.\(^6\) Changes in the insert require Supplementary NDAs, a process that resembles the initial approval of a new drug but does not require the duplication of tests already performed.\(^7\) The regulations provide that changes adding negative information (e.g., warnings or contraindications) or deleting indications "should be placed into effect at the earliest possible time."\(^8\) Drug manufacturers experience little difficulty in adding such negative information quickly.\(^9\) Positive changes (e.g., adding indications or deleting warnings) are much more difficult and expensive to make, and the company will not voluntarily initiate such modifications unless the change promises to pay for itself in increased profits.\(^10\)

\(^{42}\) See, e.g., 21 C.F.R. § 310.301 (1976).
\(^{43}\) 21 C.F.R. § 310.300(a) (1976). There is similar language in regulations on antibiotics.
\(^{45}\) Id. at § 314.8(d), (e). The manufacturer may put such changes into effect before receiving final approval of its supplementary application, provided it informs the FDA. Id.
\(^{46}\) French Interview, supra note 56; Head Interview, supra note 56. The one significant exception to the FDA's willingness to add warnings and negative information is that such information may not be given if it is associated with drug uses that the agency has not approved. The FDA feels that including such advice would imply that the unapproved use. Vodra Interview, supra note 60. This practice qualifies the value of any insert information where an unapproved use is involved.

\(^{49}\) Church Interview, supra note 56; French Interview, supra note 56; Head Interview, supra note 56. Several considerations might affect this decision. The group of potential users may be too small to justify the expense of adding the new indication. The disease may affect only a small number of persons, or a special patient population, such as pregnant women or children, that requires special tests before an indication applicable to them can be added. The manufacturer might sometimes be able to raise the price of the drug to reflect the cost of adding the new indication, but in the usual case the drug will be marketed for other uses and the new use will not require a special dosage form, so the manufacturer will not be able to raise the price without adversely affecting the drug's market position for other, more general, uses. See Kitch, The Patent System and the New Drug Application: An Evaluation of the Incentives for Private Investment in New Drug Research and Marketing in REGULATING New Drugs 81, 105 (ed. R. Landau 1973).

In addition, doctors may be prescribing the drug for the new use even without the blessing of the insert. In such a situation, adding an indication might increase a manufacturer's potential tort liability for adverse reactions resulting from the unapproved use. Proposed regulations would allow the FDA to require manufacturers who know a drug is being
The present regulations, as implemented in the procedures for creating and changing inserts, provide significant information on the level and quality of support for the various statements on a particular insert\textsuperscript{71} that a court can look to in considering the reliability of such statements as evidence. But present regulations and procedures do not provide an adequate foundation for generalizations on the reliability of the categories of insert information. Two recent developments within the FDA may provide such a foundation. First, FDA personnel plan to adopt a "drug monograph" scheme for prescription drug labeling.\textsuperscript{2} The monograph for each generic drug will contain the recommended insert for that drug. Companies wishing to market the drug with an insert differing from that in the monograph will have to submit an NDA (or Abbreviated NDA\textsuperscript{7} for approval. This scheme will encourage uniform inserts for each drug and will replace multiple individual bargaining sessions with one rulemaking proceeding. Second, the FDA has proposed a regulation\textsuperscript{74} defining the content and required support for all categories of information presented on package inserts. The proposal seeks to make inserts more adequate guides for practitioners by providing standards with regard to the kind of information that must be included under each of the specific section headings, by eliminating extraneous information which can best be obtained from published literature, by providing explicit information on indications of use, and by replacing generalities with specifics.\textsuperscript{75}

\textsuperscript{71} The manufacturer may even submit an "annotated package circular," summarizing the support for each statement on the proposed insert, as part of the NDA. 21 C.F.R. § 314.1(d) (1976) (item 9).

\textsuperscript{72} McEniry, \textit{Drug Monographs}, 29 Food, Drug & Cosm. L.J. 166 (1974); Schmidt, \textit{Communication as the Basis of Regulation}, 29 Food, Drug & Cosm. L.J. 9 (1974). The "monograph" approach developed out of necessity in the regulation of over-the-counter (OTC) drugs. Monographs outlining composition, labeling, and manufacturing standards for each "class" of OTC drugs became the basis of the agency's OTC review. See 37 Fed. Reg. 85, 9464 (1972). A monograph approach for prescription drugs that are no longer "new" was proposed in 33 Fed. Reg. 7762 (1968), and this proposal included recommended labeling for one such drug (Metyrapone).

\textsuperscript{73} 21 C.F.R. § 314.1(f) (1976).

\textsuperscript{74} 40 Fed. Reg. 15,392 (1975).

\textsuperscript{75} Id. The proposed regulations define and fill out the categories of required insert information most relevant to this comment as follows:
Indications and Usage: Specific uses of the drug are to be spelled out and distinguished as (a) the treatment, prevention or diagnosis of a recognized disease or condition or of (b) a manifestation of such disease or condition, or (c) the relief of symptoms associated with a disease or syndrome. Uses effective only in conjunction with other modes of therapy are to be labeled as such, and all indications must be supported by “substantial evidence based on well controlled investigations” as defined in 21 C.F.R. § 314.111(a)(5)(ii) (1976). Further information should indicate (a) the limits of usefulness (e.g., to particular subgroups for whom evidence is available), any tests necessary for screening patients for susceptibility, the “approximate kind, degree, and duration of improvement to be anticipated” (when available on the basis of “well controlled investigations”); (b) reservations to certain situations based on safety considerations; (c) prerequisites for long term use and differences between such use and short-term use; and (d) that there is a lack of evidence for any use which is common, or commonly believed to be effective, but which the “preponderance of evidence” indicates is ineffective. Finally, any statements of comparative efficacy or safety must also be supported by “substantial evidence” based on well controlled investigations (unless this requirement is waived). Id. at 15,396-97.

Contraindications: “[T]hose situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit” (e.g., administration to a patient with a known hypersensitivity to the drug or to a member of a group having a substantial risk of being harmed). “Known hazards and not theoretical possibilities shall be listed . . . .” Id. at 15,397.

Warnings: “[S]erious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps which should be taken if they occur.” Warnings are to be included on the basis of “reasonable evidence of an association” between the effect and the drug, regardless of whether “a causal relationship” has been “proved.” Warnings related to serious risks or hazards associated with an unapproved use may be required if such use is common. Special box warnings may be required for “special problems” leading to death or serious bodily injury; such warnings must ordinarily be based on clinical (rather than animal) data and should indicate the frequency and approximate mortality and morbidity rates for patients sustaining the reaction. Id. at 15,397.

Precautions: This is the “catchall” section of the proposed categories and contains a number of subcategories of information in addition to a “General” section. These subsections include: information to be given to the patient for safe and effective use of the drug (e.g., cautions not to drive while taking the drug); tests essential to follow the patient’s response or to detect adverse reactions; identification of clinically significant interactions which might occur with other drugs or classes of drugs in clinical use; the existence and results of studies on long term effects related to cancer, birth defects, and impairment of fertility; and information regarding use in pregnancy (six categories of information, ranging from statements that studies have established no risks under recommended dosages to contraindications for pregnant women where “the benefit-risk considerations are such that use of the drugs will never be necessary in pregnant women, i.e., when safer drugs or other forms of therapy are available.”) Id. at 15,397-98.

Adverse Reactions: “[A]n undesirable effect reasonably associated with the use of the drug, which may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.” This category includes reactions occurring with drugs “of the same chemical or pharmacological class, if applicable.” The severity, mechanism, and clinical management of important adverse reactions are to be described, and reactions are to be listed by organ system, toxicological mechanism, severity, or frequency “as appropriate.” Frequency of reactions is to be expressed either in rough estimates or, if supported by data from well controlled investigations, in percentage figures. All potentially fatal reactions are to be listed in the “warnings” or “contraindications” categories. Any comparative claims must be supported by “well controlled investigations.” Id. at 15,398.

Overdosage: “[T]he signs, symptoms and laboratory findings of overdose and the general principles of treatment” (antidotes and therapeutic measures). Id.
Congress has recently considered legislation that would continue the trends toward specificity, sophistication, and government control in the production of inserts. Proposed bills would grant the FDA more control over drug testing, prescribe stricter standards for approval of new drugs, create an additional testing phase in which the drug would be approved for use only by registered physicians who would be required to submit certain reports to the agency, require package inserts for patients using prescription drugs, allow labeling of drugs by class, establish a national compendium of drugs, and create a National Drug Review Board to advise the FDA and structure aspects of the drug approval process. The adoption of such proposals would enhance the uniformity and controls that courts could examine when assessing the reliability of insert information as evidence.

B. The Role of Inserts in Medical Practice.

Although Congress's consideration of the drug legislation of 1938 and 1962 did not focus on the medical profession and at times produced disclaimers of any intent to regulate medical practice, Dosage and Administration: Recommendations for the "usual dose, usual dosage range, and, where appropriate, an upper limit beyond which the drug should not be prescribed; dosages shall be stated for each indication when appropriate." The insert must state the "intervals recommended between dosage . . . the usual duration of treatment, and any modification of dosage needed in special patient populations," and must include "directions on dilution, preparation, and administration." Id. at 15,398-99.

The date of issuance or latest revision of the insert is to be prominently displayed. "Clinical Studies" and "References" are not to be included unless by waiver or unless cited for more detailed studies of an important subject that is of limited interest. No such reference may refer to unapproved uses. Id. at 15,399.

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S. 2697, 94th Cong., 1st Sess. 48-49 (1975) (requiring prior approval by the FDA of test protocols); H.R. 1603, 95th Cong., 1st Sess. 8-10 (1977) (requiring clinical investigators to submit reports directly to the FDA); S. 630, 95th Cong., 1st Sess. (1977) (requiring the FDA to perform the tests—at the manufacturer's expense).

S. 630, 95th Cong., 1st Sess. 13 (1977) (drugs not to be approved unless shown to possess "significantly greater safety and effectiveness" than drugs currently on the market).


Id. at 3-7.


Id.

S. 2697, 94th Cong., 1st Sess. 204-211 (1975).

Recent highly publicized challenges to the premise that the government should control drugs may lead to legislative reform that would have an opposite effect. See note 38 supra.

In response to letters from the medical community expressing concern that the bill which became the 1938 Act would interfere with the "prerogatives of the doctor," the bill's sponsor asserted that "this bill makes certain that the medical practitioner shall not be
the regulation of prescription drugs has inevitably affected the practice of medicine. At the very least, the FDA controls whether a drug will be available for doctors to prescribe. The trends toward increased sophistication and expanded government control have aggravated the tension inherent in regulating medicines while purporting not to regulate medicine. If the ultimate interest is promoting the public health and safety, it is difficult to stop at providing "the essential information the practitioner needs to use the drug safely and effectively." Once the information is there, what happens if the practitioner fails to use it?

Physicians currently view inserts with a mixture of skepticism and reliance. The American Medical Association, while recognizing inserts as one useful source of information, has repeatedly alleged that inserts are an inadequate standard for medical practice, pointing to the inconsistent purposes served by the document—advertising for the manufacturer, regulation by the government, and information for the doctor—and to the poor quality of past inserts. However, surveys of the prescribing practices of physicians indicate that package inserts (as reprinted in the Physician's Desk Reference) are now the most frequently consulted source of information on drugs, and suggest that physicians not only consult inserts, but rely on them for making decisions on dosage and administration. Medical respect for insert information varies with the
category of information involved, however. Doctors are aware of the negative bias and delay of FDA procedures, and are skeptical about the absence of indications and the mention of adverse reactions and even warnings. The growing influence of inserts may reflect the convenience of insert information and the fear of possible tort liability as much as confidence in the reliability of inserts.

The future role of inserts in medical practice will depend on the actions of the FDA and Congress. The FDA's attitude toward the role of inserts in medical practice reflects the tension inherent in the congressional attempt to regulate drugs without regulating medical practice. In prefatory comments to the proposed regulations stat-

Examination Hearings, supra note 58, at 1386. Miller distinguishes among various "stages" in the decision to prescribe a drug, and finds that the PDR is most important at the "trial" stage, when the M.D. has already become acquainted with the drug through other sources and is checking for dosages, indications, and so on. Id. at 87, 1392.

See, e.g., Haynes v. Baton Rouge General Hosp., 298 So. 2d 149, 153 (La. Ct. App. 1974) (record of testimony by expert witness disparaging the FDA and restrictions printed on "flyers").

The agency's position on the use of drugs for unapproved indications is an illustration. Several articles have pointed out examples of widespread "unapproved" uses, and others have criticized the inserts for failing to include all indications generally recognized by the medical profession. Archer, A Guide Into Chaos: Resist It, 227 J.A.M.A. 1397 (1974); Peck, FDA Approval: When Should Your Judgment Outweigh It? CURRENT PRESCRIBING, Dec. 1975, at 26; 229 J.A.M.A. 1744 (1975). In 1970 the Director of the Bureau of Drugs, Henry Simmons, suggested that doctors prescribing approved drugs for unapproved uses should submit reports to the agency so that the doctor could be given any available information on the unapproved use and so that his own experience would not be "lost." 213 J.A.M.A. 1902 (1970). The A.M.A. reacted critically to Simmons's suggestion, questioning the agency's authority to collect such data directly from doctors and the utility of such collection. 213 J.A.M.A. 1902-04 (1970). The A.M.A. argued that the "investigational or experimental status of a therapeutic agent or procedure" should be determined by medical practice, not government regulations or commercial considerations. Id. at 1904. See also Archer, Instrument or Impediment? The Regulatory Monograph in Medical Communications, 220 J.A.M.A. 1474, 1476-77 (1972).

In 1972 the FDA proposed regulations that forbid the interstate shipment of drugs "intended for uses not contained in the currently approved labeling" and require that a "manufacturer, physician, or other person who ships or requests shipment . . . in interstate commerce with the intent, or for the purpose, of an unapproved use must first file with the Food and Drug Administration an investigational new drug plan." 37 Fed. Reg. 16,504, § 130.____(a)(2) (1972). Because of limits on the FDA's jurisdiction, see 37 Fed. Reg. 15,503 (1972), the regulations announce that once a drug intended for an approved use has been shipped, the statute does not require a doctor to file an investigational new drug plan "in order to lawfully prescribe the drug for an unapproved use, when such prescribing is done as part of the practice of medicine." 37 Fed. Reg. 16,504, § 130.____(a)(3) (1972). If the unapproved use either threatens to become a public health hazard or promises a benefit, however, the regulations oblige the FDA to take one of several courses of action, including requiring the manufacturer to obtain data and conduct clinical studies to determine the safety and effectiveness of the unapproved use, changing the insert to add a warning, contraindication, indication, or restriction on prescription practices, requiring package inserts for patients, or even withdrawing approval from the drug. 37 Fed. Reg. 16,504-05, §§ 130.____(b)(1)-(8) (1972).
ing the agency's position on the legal status of package inserts and specifying the content of and support for categories of insert information, the FDA admits the limitations of the inserts and the "ultimate responsibility" of the prescribing physician, taking the position that inserts do not "control" medical standards and that the physician's tort liability should depend "upon all of the facts surrounding that use, and not upon whether or not the indication is in the package insert." Nevertheless, the FDA points out that it has been given power to control the availability of drugs from which prescribers may choose and warns that doctors departing from inserts have "the responsibility to be well informed about the drug and to base such use on a firm scientific rationale or on sound medical evidence, and to maintain adequate medical records of the drug's use and effects."

Congress is now considering legislation that would end at least part of the ambiguity over the FDA's power to regulate medical practice. Congressional committees have investigated whether doctors do or should be required to follow inserts, and some proposals would make it illegal for doctors to prescribe certain drugs for uses not mentioned on the insert without FDA approval.

C. Judicial Assessments Of Reliability

Courts considering inserts as evidence must evaluate a document prepared under a system that is still in flux. The negative bias built into the regulatory structure, more pronounced as government control has increased, makes inserts suspect as indications of good medical practice. On the other hand, the growing sophistication of inserts has increased their influence over medical practice and has encouraged the FDA and Congress to consider the inserts as a check against abuses by drug prescribers as well as drug manufacturers.

The courts can simplify their task by evaluating the standard categories of information on the insert separately. Proposed regula-

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94 37 Fed. Reg. 16,504 (1972). The proposed regulations indicate that the FDA may consider the prescription of drugs for nonapproved uses in deciding whether to find the drug unsafe and withdraw it from the market entirely.
95 40 Fed. Reg. 15,394 (1975). While most doctors would agree with at least the first of these requirements, many would consider the second unnecessary and wasteful if the use is well recognized by the profession. See 213 J.A.M.A. 1902-04 (1970).
96 See Examination Hearings, supra note 58.
tions that reflect current FDA practice make it possible to generalize about the information under each category. Courts can distinguish among the ten categories on the basis of the content and intended function of each category, the motivation of the manufacturer and the FDA to include or exclude data in each category, the support required for statements under each category, and the impact of each category on medical practice. Such generalizations and distinctions allow a court to avoid time-consuming examinations of the quality of insert evidence by developing rules based on the standard characteristics of the different categories of information.

III. THE INSERT AS HEARSAY

The argument most frequently invoked against insert evidence in the reported cases is that it should be inadmissible as hearsay. The hearsay rule prohibits the use of an insert to prove the truth of the statements it contains. Some courts have circumvented the rule by admitting inserts to prove the existence rather than the truth of their contents. Koury v. Follo demonstrates the pressures on courts to admit insert evidence in spite of its acknowledged hearsay character.

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1 See note 75 supra.

2 The division of inserts by category is not completely satisfactory. The proposed regulations indicate that some categories of information, particularly indications and precautions, may contain several types of statements requiring different levels of support. Nevertheless, the regulations will allow a court to differentiate among types of information in each category as well as among categories. See note 75 supra.


5 This pattern was suggested by dicta in Reed v. Church, 175 Va. 284, 8 S.E.2d 285 (1940), one of the earliest reported malpractice cases involving the use of a manufacturer's pamphlet against a prescribing doctor. Since the defendant doctor asserted that he had followed the procedure recommended on the pamphlet, the Virginia Supreme Court of Appeals found that he had not been prejudiced by the trial court's decision to allow the pamphlet in evidence. The court noted that "the [trial] court out of an abundance of caution gave the jury instruction . . . that they could consider the pamphlet only for the sole purpose of showing 'that Dr. Reed had knowledge of the information contained in the circular (pamphlet)." Id. at 297, 8 S.E.2d at 290.


1 See note 75 supra.

2 See note 75 supra.
In *Koury* the parents of an infant who had become totally deaf after being treated with the drug Strep-Combiotic (a compound of streptomycin and penicillin G procaine) for asthmatic bronchitis alleged that the doctor had administered an excessive amount of the drug and had failed to inform them of the hazards involved. Evidence from a medical text indicated that the dosage was excessive, and experts testified that it was sufficient to cause deafness in the child. The drug’s package insert stated: “Strep-Combiotic is contraindicated for pediatric use because there is a danger that dosages calculated to provide adequate amounts of Penicillin will, in some instances, supply excessive amounts of Streptomycin to infants and children.”

The defendant claimed to be unaware of the manufacturer's warning and introduced evidence that the drug was regularly stocked on the pediatrics ward of the hospital where the infant was treated and that the dosage prescribed was standard for pediatricians in the community. The state supreme court reversed the trial court's judgment of nonsuit, finding sufficient evidence to create a jury issue on the question of negligence. In response to the defendant's objections to the admission of the manufacturer's literature, the court agreed that the insert, like a medical text, was hearsay. Nevertheless, the court held that when inserts were used not to prove the truth of their contents, but to prove that the doctor knew or should have known certain information, the hearsay rule did not apply. Although the insert could not prove that the drug was unsafe for pediatric use, it was evidence that the doctor had been warned of the alleged danger. The doctor's disregard of this warning was “relevant upon the issue of his use of reasonable care, where other evidence shows the drug is, in fact, dangerous to the child.”

This approach does not adequately respond to the policies behind the hearsay rule. It is difficult to prevent the jury from using the insert as proof of its contents, particularly if independent medical testimony is not required. For example, in *Sanzari v.*

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107 *Id.* at 371, 158 S.E.2d at 553.
108 *Id.* at 376, 158 S.E.2d at 556.
109 *Id.* at 376, 158 S.E.2d at 556-57 (emphasis added). The limitations on the use of inserts were made explicit in the later case of Sharpe v. Pugh, 21 N.C. App. 110, 203 S.E.2d 330, aff'd without opinion by an equally divided court, 286 N.C. 209, 209 S.E.2d 456 (1974). In this suit by the parents of a child who had died of aplastic anemia after being given Chloromycetin for a viral infection, the drug inserts were the only evidence that the doctor had breached his standard of care. Despite the widely known misuse of Chloromycetin and the accompanying relaxation of the rules of evidence and liability in at least two states, see text and notes at notes 17-18 infra, the court held that it was not error to exclude the inserts from evidence. Under *Koury* insert warnings are relevant to showing that a doctor acted unreasonably only if there is independent evidence that the warnings are based on fact.
a New Jersey court using an analysis similar to that in *Koury* held that a doctor could be found negligent on the basis of insert information even without independent evidence that the information was true. Relying on the common knowledge exception to the expert testimony requirement, the court declared that "it is within the common knowledge of laymen that a reasonable man . . . who knows a drug is potentially harmful to a certain type of patient should take adequate precaution . . . ." Although the court purported to admit the insert for a purpose other than proving the standard of care, the result implicitly treats the insert information as evidence of the truth of its statement that the drug was "potentially harmful" to the patient.

The courts in *Sanzari* and *Koury* managed to reach what they considered equitable results by manipulating the technicalities of the hearsay rule. While this technique might be useful or necessary in some jurisdictions, a more straightforward approach is to analyze insert evidence in light of the policies underlying the hearsay rule. Such an analysis not only indicates whether insert information should be admissible, but also suggests what weight should be given admitted insert evidence.

Courts are hostile to hearsay evidence because the testimonial risks of sincerity, memory, perception, and narration are significant when the person who made the statement is not present, under oath, and subject to cross-examination at the trial. The sincerity risk, traditionally the strongest basis for excluding hearsay, exists when the person making a statement lacks sufficient motive to be truthful or has a motive to be untruthful, or when the circumstances

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111 Id. at 143, 167 A.2d at 633. The common knowledge exception normally applies where the need for medical judgment is minimal and lay persons are competent to resolve the negligence issue without expert assistance. See generally 1 D. LOUISELL & H. WILLIAMS, MEDICAL MALPRACTICE ¶ 8.05 (1960 & Supps.). Most cases involving the use of insert evidence do not fit comfortably within the rationale of the common knowledge exception. Inserts are prepared for experts, address technical questions, and are written in language that may require expert interpretation.


113 See McCormick, supra note 104, at § 245.
provide inadequate checks on truthfulness.\textsuperscript{114} Oath, presence, and cross-examination at trial are the usual protections against sincerity risks. The perception and memory risks reflect the possibility that a witness will not accurately perceive or recall the facts he reports.\textsuperscript{115} Cross-examination can reveal the abilities of the witness to perceive and remember and the circumstances that might affect those abilities in a particular case. Narration risks include the dangers that testimony will be misrepresented or that improper inferences will be drawn.\textsuperscript{116} Misrepresentation is not a problem when the speaker is in court and improper inferences are less likely when cross-examination is available. Hearsay evidence will normally be excluded unless special circumstances significantly reduce these testimonial risks or create a "necessity" for the testimony.\textsuperscript{117}

A. The Insert and the Testimonial Risks

An analysis of the testimonial risks associated with using inserts to prove the truth of the statements they contain is complicated by two factors. First, since inserts are prepared through a process of investigation, interpretation, reporting, and evaluation, an insert statement involves multiple hearsay with testimonial risks present at each stage of the process. Second, since the levels of required support and the motivations of the interested parties differ among the categories of information on the insert, the categories involve different testimonial risks. A useful approach is to consider the risks associated with three stages in preparing and presenting insert evidence: the gathering of data, the negotiations that lead to the contents of a particular insert, and the evaluation of the insert by the jury.

The process of collecting data involves all four testimonial risks, but the severity of the risks varies with the source of the data. These sources range from controlled studies to reports from clinical practice, depending on the category of information involved. Indications are the only category that must be supported by "well-controlled" studies. The minimum level of support necessary to publish limitations on the use of a drug, such as contraindications, warnings, precautions, or adverse reactions, ranges from

\textsuperscript{114} See Maguire, supra note 112, at 744, 765-67; Morgan, supra note 112, at 185-88.
\textsuperscript{115} See Maguire, supra note 112, at 744, 763-65; Morgan, supra note 112, at 188.
\textsuperscript{116} See Maguire, supra note 112, at 744-45, 760-63; Morgan, supra note 112, at 185-88.
\textsuperscript{117} Wigmore analyzes exceptions to the hearsay rule in terms of circumstantial probability of trustworthiness and necessity. 5 Wigmore (rev. ed. Chadbourn), supra note 104, at §§ 1420-1423.
“theoretical possibilities” to “known hazards.”

The characteristics of controlled studies reduce all four testimonial risks significantly. The statutory mandate that controlled studies be “conducted by experts qualified by scientific training and experience to evaluate the safety and effectiveness of the drug” lowers the sincerity risk. Many drug companies have the tests conducted by academic experts who are motivated to maintain their professional reputations. The designs of studies conducted by inhouse experts are subject to criticism by other experts in the FDA and should leave little room for subjective tampering with the results. Regulations on well-controlled studies lower perception risks by excluding extraneous variables, requiring a control group, and making explicit the statistical methods used to evaluate results. Immediate recording of significant data minimizes reliance on memory. Finally, regulations requiring full explanations of the test design and the methods for evaluating data combat narration risks by eliminating sources of ambiguity in interpreting the results.

Reports by practitioners lack many of these protections against the testimonial risks. Although drug companies are required to relay any adverse reaction reports they receive to the FDA, doctors are not required by federal law to report either negative or positive experiences with the drugs they prescribe. Inconvenience and the fear of malpractice suits create incentives for doctors not to report adverse reactions. These incentives suggest that the existence of adverse reaction reports is reliable on sincerity grounds while the absence of such reports may be suspect. Because of the lack of announced standards for evaluating or classifying reports from prac-

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118 See note 75 supra.
120 The FDA's capacity adequately to supervise the tests performed by manufacturers has been periodically questioned. Cf. Wall St. J., Dec. 29, 1975, at 5, col. 5 (FDA Commissioner commenting on the need for better controls on studies done by manufacturers). See generally Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975, Joint Hearings Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the Senate Comm. on the Judiciary, 94th Cong., 1st Sess. (1975). Proposed legislation would increase the FDA's control over testing. See text and notes at notes 76-83 supra.
122 Id.
123 See note 62 supra.
124 Id. Doctors involved in the testing of an “investigational new drug” (IND) are required by the drug's sponsor to report their observations, but are not required to report to the FDA. See 21 U.S.C. § 355(i) (1970); 21 C.F.R. § 312.1(a)(12), (13) (1976).
titioners, the risks of faulty perception are higher than with controlled studies. Nevertheless, doctors are trained observers, and if the drug company or the FDA receives a number of individual reports on a particular reaction, the possibility of individual errors in perception is significantly reduced. Reports from clinical experience are also likely to involve time lapses that create memory risks. The narration risks inherent in such reports might be reduced by the use of standardized reporting forms that encourage a doctor to include background data, such as case histories or patient characteristics, that could qualify his observations. As such forms become more comprehensive, however, the likelihood that doctors will take the time to fill them out decreases.126

At the negotiation stage of insert preparation the primary testimonial risk is sincerity. The drug company has conflicting motives: to sell the drug, to avoid tort liability for failure to warn, and to give basic information to physicians.127 The FDA has the announced purpose of presenting accurate information, but the general negative bias of the regulatory structure and frequent pressure from one-sided congressional investigations give the agency incentives to avoid approving indications or omitting negative information.128 In spite of the motives on each side that impeach sincerity, the whole negotiation process may be more sincere than the sum of its parts. The marketing incentives of the drug company and the cautionary posture of the FDA may lead through an adversary process to a reliable insert.129 In addition, the statutory and regulatory requirements for insert information reduce the discretion of the parties and

126 An attempt by the A.M.A. to collect reports of adverse reactions was discontinued for lack of responses in 1968. See Examination Hearings, supra note 58, pt. 1, at 320 (testimony of Dr. Sammons). In October, 1972, the FDA issued special self-addressed reporting forms and emphasized that reports would be kept confidential. In fifteen days the agency received more adverse reaction reports (1200) than in the previous six years. McEniry & Willig, The Federal Food, Drug, and Cosmetic Act and the Medical Practitioner, 29 Food, Drug & Cosm. L.J. 548, 557-58 (1974).

127 See text and notes at notes 57-58, 70 supra.

128 See text and note at note 60 supra.

129 The new drug evaluation process has been criticized in congressional hearings for relying too heavily on tests run by manufacturers who are interested in the result, and the FDA has been attacked for succumbing to industry pressures to approve drugs and indications that fail to meet statutory standards. See, e.g., Examination Hearings, supra note 58, pt. 7, at 2823-3139. The Commissioner of Food and Drugs responded to the allegations of pro-industry bias in a 900 page report in October, 1975 analyzing the testimony against the agency in detail and concluding that the FDA suffered from nothing more serious than the problems of organization and communication that beset any large bureaucracy. Comm'r of Food & Drug Admin., Commissioner's Report (Oct. 1975). The anti-industry bias created by the one-sided slant of the frequent congressional investigations may be a more serious problem, particularly in light of the limitations on the manufacturer's incentives. See note 70 supra.
thus the area where motives can influence outcomes.\textsuperscript{130} Sincerity risks vary with the category of insert information involved since different categories require different levels of support and offer different incentives to the parties.\textsuperscript{131}

When the insert, which was designed to guide doctors, is presented as evidence to laymen on juries, narration risks are likely to be the most formidable. Critics of inserts as evidence claim that a medical background is necessary to comprehend insert terminology and to recognize the limitations of the information presented.\textsuperscript{132} Unlike experts on the stand, inserts cannot aid the jury by answering hypothetical questions concerning their application to a particular case.\textsuperscript{133} Cases support the need for expert interpretation of inserts,\textsuperscript{134} but this need can be filled by the parties and by witnesses, including

\textsuperscript{130} The specificity of the proposed regulations, see note 75 supra, and the shift from an adjudicatory to a notice and hearing approach that will lead to class labeling, see text and notes at notes 72-74 supra, will make the requirements more objective.

\textsuperscript{131} Indications, which must be supported by “substantial evidence,” are considered important by the manufacturer and the FDA. Contraindications are also viewed quite seriously, and the proposed regulations require fairly strong objective evidence for this category. Warnings require less support, although boxed warnings should be distinguished from others. Adverse reactions require a low level of objective support, and doctors do not attach much importance to this section of the insert. Drug manufacturers therefore have less incentive to take this category seriously. Head Interview, supra note 56; see note 75 supra.

\textsuperscript{132} Davis Interview, supra note 56.

\textsuperscript{133} Many jurisdictions require experts to answer hypothetical questions describing the factual bases of their opinions when the experts give their opinions on fact situations that they have not personally observed. See McCOX, supra note 104, § 14. Yet only one court has mentioned that inserts are improper opinion evidence. Koury v. Folio, 272 N.C. 366, 376, 158 S.E.2d 548, 556 (1968). Hypothetical questions in theory assure that an opinion is based on an application of an expert’s knowledge to the facts of the particular case. The theory is often unworkable in practice, however, and the more progressive jurisdictions rely on cross-examination to reveal the bases for an expert’s views. McCOX, supra note 104, § 16. A similar procedure should be used with inserts. The basis for an insert’s recommendation can be found in the FDA regulations or in the FDA’s files on a particular drug. The FDA, in response to the Freedom of Information Act, 5 U.S.C. § 552 (Supp. V 1975), has recently expanded access to information in its files. Some restrictions, designed to protect trade secrets and privacy, still remain. See 21 C.F.R. §§ 312.5, 314.14, 431.70-71 (1976).

\textsuperscript{134} See, e.g., Haynes v. Baton Rouge Gen. Hosp., 298 So. 2d 149 (La. Ct. App. 1974) (insert said drug was ineffective against “most” strains of Enterobacter); Brune v. Belinkoff, 354 Mass. 102, 235 N.E.2d 793 (1968) (testimony that inserts are not meant as guides for specialists); Lhotka v. Larson, 238 N.W.2d 870 (Minn. 1976) (injections, but not oral administration of drug, contraindicated); Fisher v. Wilkinson, 382 S.W.2d 627 (Mo. 1964) (insert warned against “dermatitis” but not “exfoliative dermatitis,” a much more serious condition which had never been associated with the drug before plaintiff’s case); Crouch v. Most, 78 N.M. 406, 432 P.2d 250 (1967) (package instructions in snake-bite kit directed at the layman and not intended to bind physicians); Holland v. Stacy, 496 P.2d 1180, 1182 (Okla. 1972) (doctor testified that particular precautions applied only to patients with high blood pressure).
experts from the FDA and doctors presented by either the plaintiff or defendant.

B. Necessity: Comparative Testimonial Risks

A court deciding whether to admit insert information should consider not only the magnitude of the testimonial risks associated with the insert, but also the alternative evidence available. Some types of hearsay evidence are the best or the only evidence literally or practically available in a particular situation. If no adequate alternative can be obtained, a court may admit hearsay evidence under some exception based in part on the principle of "necessity." Two lines of argument support the "necessity" for admitting insert information. First, assuming arguendo that live expert testimony would be the better evidence, such testimony is very expensive and the "conspiracy of silence" makes medical experts unde-pendable and often unavailable to the plaintiff. Inserts are therefore necessary as a "second-best" resource. Alternatively, one can argue that the inserts are in fact superior to live expert testimony as a source of evidence and that the difficulty and expense of getting even the "second-best" live expert makes the inserts all the more important. The sources of insert information and the motives of those who prepare inserts may present fewer risks than the limited expertise and bias of a practicing doctor as a witness.

C. Exceptions to the Hearsay Rule

The exceptions to the hearsay rule correspond more or less to situations in which circumstances lowering the testimonial risks or

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135 FDA personnel are not infrequently subpoenaed to testify in suits involving inserts. Vodra Interview, supra note 60.

136 5 WIGMORE (rev. ed. Chadburn), supra note 104, § 1421, at 253; 6 J. WIGMORE, EVIDENCE § 1691 (3d ed. 1940) [hereinafter cited as WIGMORE (3d ed.)]. The paradigm case of necessity is the "unavailability" of the speaker, which is a requirement for certain of the traditional hearsay exceptions. MCCORMICK, supra note 104, § 253. See also FED. R. EVID. 804. Wigmore mentions expense as an aspect of necessity in his discussion of the learned treatise exception. 6 WIGMORE (3d ed.), supra, § 1691, at 5. Economic unavailability is not as logically appealing as physical (death) or legal (privilege, immunity from process) unavailability, but, especially when coupled with the "conspiracy of silence," it produces the same effects.

137 This argument is made in Comment, Admissibility of Medical Books in Evidence, 8 U.S.F.L. Rev. 364, 381-82 (1973) [hereinafter cited as San Francisco Comment]. See generally note 5 supra. The courts that have admitted inserts have often referred to plaintiff's difficulties in securing expert testimony. See note 25 supra.

138 Wigmore suggests this line of reasoning in discussing medical texts, arguing that doctors usually base their testimony on these sources anyway and that the text writers are better qualified, have greater incentives for accuracy, and lack the bias of a witness paid by one of the parties in a trial. 6 WIGMORE (3d ed.), supra note 136, § 1692, at 6.
creating a necessity for hearsay evidence are present. The most frequently recognized exception under which inserts are arguably admissible accepts learned treatises as evidence of the truth of their contents. This exception is based primarily on circumstantial guarantees that treatises are trustworthy, since an author generally has a strong motive to report the truth and no interest in the particular case, and opposing counsel can attack and expose out-of-date statements. In addition, such evidence may be the best available, and treatise evidence is highly probative compared to that given by most experts, who often base their opinions on treatises.

Inserts share with treatises several characteristics that underlie the treatise exception. Although inserts are prepared in part by drug manufacturers, who, unlike text writers, may have suspect motives as potential parties in litigation, the influence of any bias is checked by the countervailing motives of the manufacturer, the participation of the FDA, and the regulatory requirements for objective support. Trial counsel can challenge out-of-date inserts, and the FDA has increased efforts to ensure that inserts are kept current. The necessity for inserts is the same as that for treatises, and inserts have a high evidentiary value as compared to testimony by medical experts.

Treatment as learned treatises would not mean universal admissibility for inserts, however. Medical treatises are admissible as direct evidence in only two jurisdictions by case law and a few others by statute. In most other jurisdictions, treatises are admis-

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139 Most exceptions were created without being explained in terms of rational principles, and even in the modern codes, the exceptions do not match the rationales exactly. See Mccormick, supra note 104, §§ 244-245, at 579-84; 6 Wigmore (rev. ed. Chadbourne), supra note 104, § 1420, at 252.
140 See Fed. R. Evid. 803(18); Mccormick, supra note 104, § 321; 6 Wigmore (3d ed.), supra note 136, §§ 1690-1700; Holz, Learned Treatises As Evidence in Wisconsin, 51 Marq. L. Rev. 271 (1967); 66 Mich. L. Rev. 183 (1967); San Francisco Comment, supra note 137.
142 Id. § 1691, at 5.
143 Id.; see Stoudenmeier v. Williamson, 29 Ala. 558, 567 (1857).
145 See text and notes at notes 119-31 supra.
146 See 40 Fed. Reg. 15,392, 15,396, 15,399 (1975) (proposed §§ 1.106(b)(5), 1.112(d)).
147 Inserts are created by the party with the most comprehensive information about the drug and are consulted more often than any source by prescribing doctors. See text and notes at notes 90-91 supra.
sible to a greater or lesser degree during cross-examination. Even where admissible, treatises are usually restricted to supporting or impeaching expert testimony and are not considered as independent substantive evidence. These limitations are justified in part by narration risks; because of the fear that the jury will be misled unless the treatise is interpreted by an expert, admissibility is limited to situations where an expert is on the stand and available to testify. In addition, before any treatise can be admitted, it must be proved to be a "standard authority" in the field. This requirement helps guarantee reliability and guards against judging a doctor by a standard not available to him.

Some of these limitations are unnecessary for inserts. Inserts are readily available to all doctors and are consulted more often for guidance in prescription decisions than any "standard" text. Although the narration risks associated with inserts are more difficult to distinguish from those accompanying treatises, most courts that have admitted inserts have not imposed the limitations that attach to treatises. The insert statements have either seemed sufficiently clear or the available experts have provided adequate interpretations.

Another hearsay exception that might apply to inserts is that when the legislature replaced it with one based on rule 803(18) of the then Proposed Federal Rules of Evidence (allowing admissibility "To the extent called to the attention of an expert witness upon cross-examination or relied upon by him in direct examination"). Nev. Rev. Stat. § 51.255 (1973); see Note, Overcoming the Conspiracy of Silence, supra note 6, at 1024-40; 84 A.L.R.2d 1338, 1347-50 (1962).

151 See McCormick, supra note 104, § 321, at 743-44.
153 See, e.g., Fed. R. Evid. 803(18); Adv. Comm. Notes, supra note 112, at 316-17. This concern is also reflected in rules allowing texts to be read aloud but not to be carried into the jury room as physical exhibits. Id.
154 Fed. R. Evid. 803(18) adopts a liberal approach in allowing a text to be "established as a reliable authority by the testimony or admission of the witness or by other expert testimony or by judicial notice." Overly strict requirements for establishing that a work is a "recognized authority" can destroy the utility of texts as weapons against the "conspiracy of silence." For an example of the difficulty of eliciting the required testimony from a hostile witness, see Conason, Medical Cross-Examination—Refusal to Recognize Medical Authorities, 10 Trial Law Q., Spring, 1974, at 29.
155 The general trend of the case law is described in Merrill, supra note 3, at 52-65; Pruzan, supra note 7, at 729-32. Most courts do not explicitly articulate their reasons for distinguishing between the admissibility of inserts and the admissibility of medical texts. An exception is the court in Mueller v. Mueller, 221 N.W. 39, 42-43 (S.D. 1974), which mentioned the rapid development in the field of drugs, the rigorous testing required by the government, the potential liability of drug manufacturers, and the limits on doctor time and expertise to justify admitting an insert.
for public records and reports. Evidence admitted under this exception is not subject to the limitations governing treatise evidence, but extending the public reports exception to cover inserts is more problematic. The common law and statutory exception for public records is based on "the assumption that a public official will perform his duty properly and the likelihood that he will remember details independently of the record," an assumption complicated by the many public and private participants in insert preparation. Inserts might come within a recent expansion of the exception in rule 803(8) of the Federal Rules of Evidence to include "evaluative reports." The admission of such reports is the most controversial aspect of the public records exception, however, and the scope of the exception is still uncertain. Inserts seem to fit within the terms of rule 803(8) as "factual findings resulting from an investigation made pursuant to authority granted by law," but even if inserts qualify as evaluative reports, the Advisory Committee Notes recommend that such evidence be excluded if "the sources of information or other circumstances indicate lack of trustworthiness." The controls built into the data gathering process and the adversary nature of the negotiations to prepare the inserts may provide sufficient indicia of reliability to withstand exclusion under this provision.

Even if inserts do not fit within any recognized exceptions, a court may admit them by creating a new exception on the basis of the policies behind the hearsay rule. The Federal Rules of Evidence codify this possibility and suggest the relevant considerations in a special provision for admitting hearsay evidence not specifically covered by any of the foregoing [recognized] exceptions but having equivalent circumstantial guarantees of trustworthiness, if the court determines that (A) the statement is offered as evidence of a material fact; (B) the statement is

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158 McCormick, supra note 104, § 317, at 737-38.


160 Fed. R. Evid. 803(8)(c). The Advisory Committee Note suggests the following factors as indicative of trustworthiness: "(1) the timeliness of the investigation . . . ; (2) the special skill or experience of the official . . . ; (3) whether a hearing was held and the level at which conducted . . . ; (4) possible motivation problems . . . ." Advisory Comm. Notes, supra note 112, at 313. These factors suggest an analysis in terms of the testimonial risks of sincerity, memory, perception, and narration.
more probative on the point for which it is offered than any other evidence which the proponent can procure through reasonable efforts; and (C) the general purposes of these rules and the interests of justice will best be served by admission of the statement into evidence.\textsuperscript{161}

This rule articulates the two basic criteria applied to inserts above: the presence of testimonial risks—"equivalent circumstantial guarantees of trustworthiness" and serving "the general purposes of these rules"—and necessity—high probative value compared to reasonably available alternative sources of evidence.\textsuperscript{162}

The analysis of insert evidence in terms of these criteria indicates that admitting inserts would be consistent with the policies underlying the hearsay rule. The probative value and availability of inserts are high compared to the practical alternative sources of evidence, and the trier of fact will be aided in its determinations if all relevant and material insert information is admitted. The regulated insert preparation process substantially reduces the testimonial risks, and the insert can be challenged by an investigation into its foundations or the presentation of contradictory evidence.\textsuperscript{163} The insert categories based on inference or reports from clinical experience, rather than controlled studies, carry higher testimonial risks, but more probative evidence on these points is difficult to obtain. Rather than excluding any category of insert information as hearsay, a court should take account of the differences in the probative value and testimonial risks associated with the various categories when determining what role each category should play as evidence of the standard of care or causation.

IV. THE INSERT AS EVIDENCE OF THE STANDARD OF CARE

Overcoming the hearsay objection does not by itself guarantee that an insert statement will be admitted as evidence of the stan-

\textsuperscript{161} \textit{Fed. R. Evid.} 803(24), 804(5) (same language).

\textsuperscript{162} The concern for the "interests of justice" appears to allow a court discretion to consider policy issues apart from the hearsay rule.

\textsuperscript{163} The quality of an opposing party's challenge to insert evidence will depend on the admissibility and availability of such sources as FDA records, manufacturers' records, medical texts, articles, and doctors' records. Some sources, such as the testimony of live experts, hospital records, and medical treatises, may be independently admissible as direct evidence. \textit{See} McCormick, \textit{supra} note 104, § 313; text and notes at notes 140-54 \textit{supra}. Others, such as journal articles, are normally excluded. \textit{See}, e.g., Nolan v. Dillon, 261 Md. 516, 276 A.2d 36 (1971). The FDA maintains some restraints on access to its files. \textit{See} note 133 \textit{supra}. While allowing extensive investigation into the data supporting insert statements would lower the hearsay risks, such an exercise could expand the possibilities for delay and confuse the jury.
standard of care. The relevance and admissibility of insert information depend on how a court defines the standard of care and on whether insert evidence can be accommodated with the policies and conceptual framework that underlie that definition.

A. The Traditional Rules: Policies and Problems

Courts have traditionally held that the standard of care in medical malpractice trials is established by the customary practice of doctors as proved by expert testimony. The most important justification advanced for this approach is that the standards accepted as good medical practice by a significant portion of the profession are likely to be sounder than standards set by judges or juries. Judicial tribunals allegedly lack the experience and competence to assess the wisdom of technical decisions involving a high degree of judgment and to distinguish between negligent and nonnegligent errors of judgment. Legislatures also generally defer to the medical profession rather than using statutes or administrative agencies to define good medical practice in particular situations. This deference reflects the concern that legislative or administrative stan-

184 See, e.g., McCoid, supra note 6; Morris, Custom and Negligence, 42 COLUM. L. REV. 1147, 1163-67 (1942); Note, Malpractice and Medical Testimony, supra note 6; Annot., 81 A.L.R.2d 597 (1962). Definitions of the relevant class of doctors vary, and courts recognize practices accepted by respectable minorities in the profession and allow for extraordinary circumstances. See 1 LOUISELL & WILLIAMS, supra note 111, ¶¶ 8.04-06. Currently recognized exceptions to the professional standard rule are discussed in note 175 infra.

185 It has also been urged that the doctor-patient relationship is essentially a consensual one and that the community standard of care reflects the reasonable expectations and desires of the parties more accurately than any substitute standard established by such intervention could. See Epstein, supra note 6.

186 See McCoid, supra note 164, at 605-09; Morris, supra note 6, at 1163-67. The most notorious recent case of judicial standard setting is Helling v. Carey, 83 Wash. 2d 514, 519 P.2d 981 (1974), where the court determined that the defendant ophthalmologist was negligent as a matter of law for failing to give the plaintiff a pressure test for glaucoma although the trial court had found that the uniform practice of the profession was not to give such tests to persons of the plaintiff's age and condition. The state legislature responded by passing WASH. REV. CODE § 4.24.290 (Supp. 1975), which purported to reestablish the professional standard. See Bradford, A Unique Decision, J. LEG. MED., Sept./Oct. 1974, at 35; Epstein, supra note 6, at 108-113; 20 N.Y.L.F. 669 (1975); 51 WASH. L. REV. 167 (1975).

187 See e.g., ILL. REV. STAT. ch. 91 (1975). Regulation of medical practice has thus far been left to the states by the federal government, though present national health insurance programs for certain groups have resulted in some modifications of this generalization, primarily to deal with inefficient or fraudulent use of government funds. See Comment, PSRO: Malpractice Liability and the Impact of the Civil Immunity Clause, 62 GEO. L.J. 1499 (1974); Note, Federally Imposed Self-Regulation of Medical Practice: A Critique of the Professional Standards Review Organization, 42 GEO. WASH. L. REV. 822 (1974); Note, PSRO: A Status Report on Medical Peer Review Under the 1972 Social Security Act Amendments, 6 LOY. CHI. L. REV. 90 (1975). But cf. 42 U.S.C. § 1395 (1970) (disclaiming intent to regulate medical practice in program providing health insurance for the aged).
standards would prove inflexible or unworkable and would not necessarily improve the quality of medical care.188

Reliance on the standard practice of the profession as proved by experts may also promote administrative efficiency. Rather than determining a scientifically correct standard and permissible deviations, the trier of fact decides only whether the defendant's conduct met a standard defined by expert witnesses, whose testimony the procedures of the court are designed to evaluate. Even when conflicting testimony produces a "battle of the experts," the evidence is limited to the issue of defining the professional standard; the courts avoid becoming forums for determining scientific truth—a function they are ill-suited to perform. The professional standard rule and the expert testimony requirement also operate as devices for controlling juries in a context where a sympathy-provoking plaintiff, whose suffering may result from his illness rather than the doctor's negligence and who benefits from hindsight, faces a presumably insured doctor who had to make a judgment under uncertain conditions and whose reputation and livelihood are at stake.189 Limiting the standard of care issue to questions a jury can comprehend and appropriately decide reduces the potential for confusion that might encourage the trier of fact to decide on the basis of immaterial considerations. Requiring expert testimony provides an even more direct check on the jury's discretion.

The traditional rules have their critics. Plaintiffs complain about the difficulty and expense of acquiring expert testimony. The stated justifications for the professional standard of care rule are open to question, particularly when a doctor's decision involves prescription drugs. Commentators170 and witnesses in congressional hearings171 have challenged the soundness of customary prescribing practices.172 The more extreme allegations that the misuse of drugs

188 See Epstein, supra note 6, at 107 & n.43.
189 See Morris, supra note 164, at 1165.
171 E.g., Examination Hearings, supra note 58.
172 Alleged abuses include prescribing without taking a culture to determine the identity of the disease and the effectiveness of the drug, prescribing without an examination, prescribing a drug that is contraindicated or that can do nothing for the patient's problem, and prescribing for unnecessary prophylactic purposes. See generally H. Dowling, MEDICINES FOR MAN 276-83 (1970).
by medical professionals has reached crisis proportions are probably
exaggerations, but the cases involving package inserts indicate
that the improper use of at least some drugs has been widespread.
The judicial efficiency and jury control justifications for the tradi-
tional rules are also subject to attack outside the prescription drug
context. Insured defendants accused of negligence often face seri-
ously injured plaintiffs in nonmedical tort suits involving highly
technical issues without such special rules. Moreover, the current
cost of malpractice litigation, and the confusion generated by con-
flicting expert testimony, suggest that the traditional rules have had
only limited success in achieving efficiency and objectivity.

B. The Use of Inserts: Possibilities and Policies

Courts willing to allow inserts a properly circumscribed role as
evidence of the standard of care may be able to alleviate some of
the problems created by the traditional rules without seriously jeop-
ardizing the policies underlying those rules—encouraging sound
medical practice, promoting efficiency, and checking the discretion
of the jury. The potential value of insert evidence on the standard
of care in a particular case depends on the nature of the medical
decision in question and the characteristics of the insert information
relevant to that decision.

Insert information is relevant to at least three of the four gen-
eral types of decisions doctors make in prescribing drugs. Plaintiffs
have introduced insert evidence to challenge doctors' determina-
tions of what drug, if any, should be prescribed, how a drug should

173 See, e.g., Melmon, Sheiner & Rosenberg, supra note 170.
174 See, e.g., Incollingv. Ewing, 444 Pa. 263, 282 A.2d 206 (1971); text and notes at notes
176-79 infra. Possible reasons for such abuse include the pressures put on doctors by patients
and drug promoters; see, e.g., Muller, The Overmedicated Society: Forces in the Marketplace
for Medical Care, 176 SCIENCE 489 (1972); The Peculiar Success of Chloromycetin, supra note
18, the asserted inadequacy of medical education in clinical pharmacology, see TASK FORCE
ON PRESCRIPTION DRUGS, U.S. DEP'T OF HEALTH, EDUCATION & WELFARE BACKGROUND PAPERS:
THE DRUG PRESCRIBERS (1968); DOWLING, supra note 172, at 271-72, and the overwhelming
amount of information on current changes in drugs. See DOWLING, supra, at 289-90.

175 Courts have already created and expanded exceptions to the special rules in cases
where the reasons for the special rules seem inapplicable. The most common titles for these
exceptions are "res ipsa loquitur" and "common knowledge," but the techniques courts use
are more varied than these two titles suggest. See Note, Malpractice and Medical Testimony,
supra note 6, at 343-49 (1963); Note, An Evaluation of Changes in the Medical Standard of
Care, supra note 6, at 744-47 (1970); Res Ipsa Loquitur: Its Place in Medical Malpractice
Litigation, 8 U.S.F.L. Rev. 343 (1973). There is no consensus on the boundaries of these
exceptions, and decisions have been criticized for overestimating the competence of juries,
see McCoid, supra note 6, at 632; Epstein, supra note 6, at 114-15, and judges, see note 166
supra, to make sound decisions in superficially "obvious" cases.
176 This decision involves balancing the costs and benefits of using a particular drug
be administered,\textsuperscript{177} and what information should be disclosed to a

\begin{itemize}
  \item (probability and character of the desired results, the chances and severity of adverse reactions for a particular patient) and the costs and benefits of alternative therapies (other drugs, nondrug therapies, no treatment).
  \item Several cases have involved the prescription of Chloromycetin for colds (against which it is ineffective) and for minor infections in spite of special warnings that the drug should be used only for particular conditions, e.g., typhoid fever, which are life-threatening and respond poorly to safer treatments. See, e.g., Stottlemire v. Cawood, 213 F. Supp. 897 (D.D.C. 1963); Mulder v. Parke Davis & Co., 288 Minn. 332, 181 N.W.2d 882 (1970); Sharpe v. Pugh, 270 N.C. 598, 155 S.E.2d 108 (1967); Incollingo v. Ewing, 444 Pa. 263, 282 A.2d 206 (1971). Other cases involving alleged misprescription of drugs include: Meier v. Ross Gen. Hosp., 67 Cal. Rptr. 471 (Dist. Ct. App.), rev'd, 69 Cal. 2d 420, 445 P.2d 519, 71 Cal. Rptr. 903 (1968) (use of tranquilizer contraindicated for severely depressed patients); Haynes v. Baton Rouge Gen. Hosp., 238 So. 2d 149 (La. Ct. App. 1974) (drug used to combat strain of bacteria against which insert said it was ineffective); Sanzari v. Rosenfeld, 34 N.J. 128, 167 A.2d 625 (1961) (drug which could cause dizziness and loss of equilibrium used when doctor allegedly knew other drugs would work); Trogun v. Fruchtman, 58 Wis. 2d 669, 207 N.W.2d 297 (1973) (patient with positive tuberculosis test given drug allegedly unsafe for such patients). See also Short v. Downs, 537 P.2d 754 (Colo. App. 1975) (drug labeled “not for human use” used for breast augmentation); Ruden v. Hansen, 206 N.W.2d 713 (Iowa 1973) (pregnant hogs given vaccine when insert contraindicated vaccination during pregnancy).

\textsuperscript{177} Administering a drug requires decisions on proper dosage and routes of administration (e.g., oral, intravenous injection, intramuscular injection) and on what precautions (e.g., sensitivity tests, questions about allergies) should be observed.


Cases where a failure to take proper precautions was alleged include: Chrestman v. Kendall, 247 Ark. 802, 448 S.W.2d 22 (1969) (patient became permanently deaf when doctor
On the other hand, inserts are at best tangentially relevant to a doctor's diagnosis of a patient's illness.\(^{178}\)

This comment's examination of the insert preparation process and of the hearsay risks associated with insert evidence has demonstrated that the various categories of insert information are not equally relevant or probative as evidence of the proper standard of care. Categories differ not only in reliability, but also in the type of

\(^{177}\) See Sharpe v. Pugh, 270 N.C. 598, 155 S.E.2d 108 (1967) (alleged negligent prescription of chloromycetin). The court held that "it would be negligent if defendant prescribed, as a remedy for which it was neither necessary nor suited, a drug which he knew or should have known was dangerous, without advising and warning Brenda's parents of the possible or probable injurious effects from the use thereof." Id. at 605, 155 S.E.2d at 113. On remand, the only evidence that Chloromycetin was "neither necessary nor suited" for the use in question was contained in the manufacturer's literature. The trial court directed a verdict for the defendant. Since, according to Koury v. Follo, 272 N.C. 366, 158 S.E.2d 548 (1968), see text and notes 106-09 supra, such literature could not be admitted to prove the truth of its contents, the court of appeals held plaintiff's evidence insufficient on the issue of negligent disclosure. Sharpe v. Pugh, 21 N.C. App. 110, 203 S.E.2d 330 (Ct. App.), aff'd by an equally divided court, 286 N.C. 209, 209 S.E.2d 456 (1974).

For other cases on informed consent to treatment with prescription drugs, see Marsh v. Arnold, 446 S.W.2d 949 (Tex. Civ. App. 1969); Trogun v. Fruchtmann, 58 Wis. 2d 569, 592-604, 207 N.W.2d 297, 309-15 (1973) (court considered the most recent cases on informed consent and held that plaintiff must establish known risks by expert testimony). See generally note 6 supra.

\(^{178}\) Insert information describing the symptoms of the condition for which a drug is indicated may be relevant to the correctness of a doctor's diagnosis, but diagnosis decisions usually involve a high degree of medical judgment, and inserts are likely to be less valuable for diagnosis decisions than for treatment decisions. Distinguishing between diagnosis and treatment may be difficult, however. Doctors sometimes use drugs that are effective against a broad range of infections without isolating the one causing a patient's problem. This practice has been criticized by some as irresponsible, 227 J.A.M.A. 1030, 1031 (1974), and defended by others as efficient, 227 J.A.M.A. 1029 (1974). In addition, if doctors know that their judgment in diagnosis will be treated with more deference than their judgment in treatment, they may adjust their diagnosis decisions to give them maximum leeway in treatment. This phenomenon has already appeared in at least one case involving the use of penicillin for mumps. The defendant doctor testified that penicillin was not therapeutic for mumps. Defendant's record showed he had administered the drug "for mumps," but a "?" and "& pharyngitis" had been added by a different pen. Rotan v. Greenbaum, 273 F.2d 830 (D.C. Cir. 1959). It has also been reported that doctors who believe a drug is useful for treating symptoms not listed on the insert cover themselves by listing on their patients' charts symptoms for which the drug is indicated on the insert. Peck, supra note 93, at 26.
advice they give practitioners. Some insert information provides data on costs or benefits that a doctor can balance with other data when making his decision. For example, warnings and adverse reactions describe the nature—though not usually the probability—of the potential costs of using a drug; and indications list the uses of a drug supported by substantial evidence of effectiveness, but usually do not mention its effectiveness as compared to alternative treatments. Other insert information suggests possible actions without implying that these suggestions exhaust the reasonable alternatives. For example, instructions on dosage often indicate the amount of a drug normally necessary to produce the desired effect; adverse reactions and warnings suggest information that might be disclosed to patients; and indications list some, but arguably not all, legitimate uses of a drug. Finally, some insert information makes recommendations that purport to establish the boundaries of reasonable medical practice. For example, a drug is contraindicated where the FDA determines that the potential costs of using it outweigh any possible benefits; and some precautions and warnings recommend that a doctor acquire certain data or run sensitivity tests on a patient before administering the drug.

The type of advice given reflects the limitations of inserts as guides for medical decisions. Boundary-setting recommendations are generally limited to decisions that can be made on the basis of the objective data available to the FDA without the need for a treating doctor's judgment. For example, a case-by-case balancing of patient characteristics and circumstances is unnecessary to determine that Chloromycetin (the drug involved in Mulder) should not be given for a cold. For decisions that require more doctor judgment because the factors involved are more complex, less objectively quantifiable, or more evenly balanced, inserts provide information and may make suggestions, but the decision rests more completely within the doctor's discretion.

Courts desiring to allow inserts a significant role as evidence of the standard of care can protect the policies behind the professional standards rule, the expert testimony requirement, and the hearsay rule by limiting the categories of insert information to the evidentiary uses for which they are reliable and appropriate. The insert statements most appealing as independent evidence of the proper standard of care are those from reliable categories that make clear and apparently definitive recommendations on decisions that re-

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180 See note 75 supra.
quire minimal judgment on the part of the treating doctor. The strongest statements in terms of these criteria are contraindications—clear recommendations against use based on weighing known risks against any possible benefit. Warnings that limit the use of drugs, precautions that require certain tests or procedures, and limitations on safe dosage levels also fit the criteria, but such recommendations are more questionable because the level of support they require is not specified. Indications are supported by the most reliable data, but must be read in light of the limiting information on an insert (a task an expert should perform) and do not usually take account of the alternative treatments that are relevant to a prescription decision. The absence of an indication is not a clear recommendation and does not reflect reliable support. Instructions on normal dosage and administration make clear recommendations, but their reliability may be questionable, and the potential for case-by-case variance is high. Adverse reactions, warnings that list serious hazards, and precautions that give information on carcinogenicity do not make recommendations, but rather provide information on the costs of a given decision. One-sided information on benefits and costs may appropriately serve as the basis for an expert’s balancing, but is not designed to be weighed by lay people without expert assistance.

C. The Use of Inserts: Alternative Approaches

The potential value of an insert statement in terms of encouraging sound medical practice, promoting judicial efficiency, and checking the discretion of jurors does not by itself determine the relevance of insert evidence to the negligence issue. A threshold question is how the law defines the standard of care. Several courts have admitted inserts as evidence on the negligence issue, but few have expressly considered how to integrate this new evidence with the prevailing definition of the standard of care. The significance of insert evidence will depend on whether the standard of care continues to be defined by professional practice, is identified with the insert itself, or is determined by a jury or a judge choosing on some basis between these two alternatives. Three alternative ways in which courts might accommodate the definition of the standard of care with insert evidence on the negligence issue are suggested by current approaches to the standard and the case law on insert evidence.

1. *Maintaining the Professional Standard Rule.* In a jurisdiction that defines the standard of care by current professional prac-
tice, inserts are relevant evidence of the standard only if it can be proved that medical practice conforms to their recommendations. The question is not whether inserts are reliable guides, but whether a significant number of doctors actually follow them. The testimonial risks are not a problem, since the insert is being used to prove only that it makes a recommendation, not that the recommendation is reliable.

If the professional standard must be proved by expert testimony, the insert can be influential only as a basis for an expert's opinion. If a court relaxes this requirement to allow inserts as independent evidence of the professional standard, an insert's significance will depend on the foundation necessary to show that an insert statement is relevant to current medical practice. To require that a qualified expert must testify that the professional practice in the community is identical to a particular insert recommendation would severely restrict the insert's value as a weapon against the "conspiracy of silence." While any insert evidence admitted with such a foundation may seem mere surplusage, it could have an important impact on a jury if the expert testimony on the standard of care is conflicting.

Inserts would play a more significant role if courts admitted them on the basis of testimony by less qualified experts or statistical evidence that doctors normally follow inserts in the absence of special expertise with a drug or unusual circumstances. This approach, which was followed by the Minnesota Supreme Court in Mulder v. Parke Davis & Co. in its first opinion, could substantially erode the expert testimony requirement and alleviate the "conspiracy of silence." General evidence that doctors follow inserts, however, without reference to a particular drug or a particular category of insert information, is not very strong proof of the professional standard for a particular decision. In addition, a jury may confuse the issue of what doctors actually do with what the jurors feel doctors should do.

2. The Insert as a Burden-Shifting Device. A second approach would allow a plaintiff who can prove that his doctor departed from certain insert recommendations to shift to the defendant the burden of either proving or producing evidence of compliance with the customary practice of the profession. The insert would not serve as

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181 See note 105 supra.
184 Cf. McCoid, supra note 6, at 632 (recommending that defendant have burden of going forward if plaintiff has introduced persuasive non-expert testimony).
evidence of the proper standard of care, and its reliability would not be open to attack. This approach preserves the advantages of looking to professional practice for the ultimate standard, but also attacks the "conspiracy of silence" problem by placing the burden of producing expert testimony on the party with the best access to experts. Requiring the plaintiff to prove a departure from an insert recommendation diminishes the potential for frivolous suits.

The burden-shifting procedure involves several difficulties. Although the insert is not intended to serve as evidence of the standard of care, an implicit judgment that an insert represents a prima facie standard is necessary to justify the burden-shifting function. Unless the insert is superior evidence, it is unclear why courts should allow this function to inserts rather than medical treatises, journal articles, and other materials. This comment's analysis of inserts indicates that certain categories of insert information are superior to alternative materials, but suggests that only the more reliable recommendations that purport to define the standard of care should qualify to shift the burden. Proving a departure from an insert recommendation may also raise a problem. The benefits of the burden-shifting procedure will be compromised if a plaintiff needs expert testimony to prove a departure. Most recommendations that purport to define standard medical practice are fairly clear, however, and in any event the pool of experts qualified to interpret inserts includes FDA officials and doctors outside the community.

A more difficult problem is to adjust the consequences of shifting the burden so that the procedure will achieve its purpose without attaching undue weight to the insert evidence. Shifting the burden of producing evidence while leaving the burden of proof on the plaintiff will not help a plaintiff who has no expert; a doctor may be able to get a summary judgment or a directed verdict by simply testifying that his actions met the customary standard. Such testimony should be an adequate defense as a matter of law unless the departure from the insert is evidence of the standard of care, rather than a mere burden-shifting device. Shifting the burden of proof to the defendant might allow more cases to get to the jury, on the ground that the jury could reasonably disbelieve the testimony of the doctor or his experts. This approach makes it difficult to confine the jury's use of the insert, however; a doctor's departure from

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185 See text and notes at notes 132-35 supra.
186 A court's standard for granting a directed verdict will determine the potential impact of shifting the burden of proof when the plaintiff has no expert testimony.
an insert is likely to influence a jury’s evaluation of the defendant’s evidence, regardless of the court’s instructions.

A final question raised by the burden-shifting procedure is whether the burden should shift when the plaintiff has expert testimony other than the insert to support his case. If the procedure is designed only to assist plaintiffs who cannot get experts, it may seem unnecessary when the plaintiff has an expert. On the other hand, the plaintiff may still be suffering a relative disadvantage in access to experts, and it seems anomalous to deny a plaintiff with a presumably stronger case the advantages granted to those unable to get experts. However, since the plaintiff’s disadvantage is less severe in such a case, shifting the burden of proof is more difficult to justify without an implied assumption that medical practice will improve if certain insert recommendations create a prima facie standard of care. If doctors perceive that insert recommendations will play an important role in allocating burdens of proof in malpractice trials, the customary practice of the profession may tend to become indistinguishable from the relevant insert recommendations.\textsuperscript{187} If this tendency were to become pronounced, the effects of a burden-shifting approach would approach those of treating departures from inserts as direct evidence of negligence.

3. The Insert as a Prima Facie Standard of Care. In Mulder v. Parke Davis & Co.\textsuperscript{188} the court formulated a set of rules creating an exception to the professional standard of care rule to allow a plaintiff to prove a prima facie breach of the standard of care by showing that his doctor deviated from certain insert recommendations.\textsuperscript{189} The burden then shifts to the defendant to justify or excuse

\textsuperscript{187} Cf., e.g., Methylprednisolone for Sunburn, FDA and Package Insert Notwithstanding, 225 J.A.M.A. 72 (1973) (letter from doctor concerned about legal implications of using a drug for a purpose not on the insert); Peck, supra note 93, at 28 (cautions physician against the risk of departing from the insert under present law).

\textsuperscript{188} 288 Minn. 332, 181 N.W.2d 882 (1970); see text and notes at notes 19-25 supra.

\textsuperscript{189} The plaintiff must presumably lay a proper foundation for the insert he seeks to use, including a demonstration that the insert was current and available to the prescribing doctor when the allegedly negligent act occurred. See Carmichael v. Reitz, 17 Cal. App. 3d 958, 95 Cal. Rptr. 381 (Dist. Ct. App. 1971); note 10 supra. The plaintiff must also prove that the defendant deviated from a material insert recommendation, a task that may require expert testimony. See text and notes at notes 132-35 supra. In addition, the Mulder opinion requires the plaintiff, as a condition of establishing the doctor’s prima facie negligence, to prove by “competent medical testimony” that the doctor’s deviation caused the injury. This requirement confuses the issues of standard of care and causation and has been deleted by the courts that have followed Mulder. See note 27 supra. Requiring expert testimony to prove causation may undercut Mulder’s liberalizing effect on the standard of care. See text and note at note 225 infra.
his deviation. This procedure's impact on the policies underlying the professional standard rule and its success in combating the effects of the "conspiracy of silence" will depend on what types of insert information are allowed to define the prima facie standard of care and what defenses are allowed to justify or excuse a departure from the standard.

The Mulder opinion mentions several types of insert recommendations as standard-setters, but does not explain why they were selected. If a court restricts the relevant recommendations to those such as contraindications, that are in reliable categories and make clear recommendations on decisions that do not require a treating doctor's judgment, the impact on sound medical practice would not be severe even if only minimal defenses were available. If weaker recommendations, such as indications or warnings, are allowed to set the standard, the nature of possible defenses becomes more critical.

The Mulder opinion stops short of making any recommendation conclusive on the negligence issue; the doctor always has a chance

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190 Compare Mulder with Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 317 P.2d 170 (Dist. Ct. App. 1957), in which the plaintiff alleged that excessive amounts of a drug administered in a diagnostic proceeding had paralyzed him. The court held that insert information on proper dosage was admissible, but rejected a trial court instruction suggesting that a departure from the insert might by itself constitute experimentation which would be negligent unless the patient had given his informed consent: "The mere fact of departure from the manufacturer's recommendation where such departure is customarily followed by physicians of standing in the locality does not make that departure an 'experiment.'" Id. at 575-76, 317 P.2d at 180. See also Julien v. Barker, 75 Idaho 413, 423, 272 P.2d 718, 724 (1954) (insert information provides "prima facie proof of a proper method of use, given by the maker, which must be presumed qualified to give directions for its use and warnings of any danger therein").

191 The Mulder procedure appears to depart dramatically from the policy of deferring to the presumed wisdom of current medical practice. Previous exceptions to the professional standard and expert testimony rules have been made in cases where a court has determined that the medical judgment factor is minimal and where laypersons are competent to resolve the negligence issue without expert assistance. See note 175 supra. In such cases the reasonable person standard replaces the professional standard. Although at least one court has held that information from an insert was adequate to bring the medical decision in question within the common knowledge of the jury, Sanzari v. Rosenfeld, 34 N.J. 128, 143, 167 A.2d 625, 633 (1961), most cases involving the use of insert evidence do not fit comfortably within the rationale of the common knowledge exception. See text and note at note 111 supra.

192 Where a drug manufacturer recommends to the medical profession (1) the conditions under which its drug should be prescribed; (2) the disorders it is designed to relieve; (3) the precautionary measures which should be observed; and (4) warns of the dangers which are inherent in its use, a doctor's deviation from such recommendations is prima facie evidence of negligence.

288 Minn. at 339-40, 181 N.W.2d at 887.

193 This reluctance to eliminate the doctor's discretion is sound. Even contraindications are subject to the limited foresight and possible bias of the insert preparers.
to defend his departure from the recommendation. But the court
gives no real guidance on what defenses are available. While the
Mulder procedure in effect shifts the burden of proof on the stan-
dard of care issue to the defendant, it differs from the simple
burden-shifting approach discussed above in not expressly adhering
to the professional standard rule in evaluating a doctor's defenses.
The court does not mention any specific defenses, but declares that
a doctor must give the reasons for his deviations and that the jury
will normally determine whether the reasons justify or excuse the
doctor's action. The court adds that "[t]here may be situations
where as a matter of law the explanation exonerates [the doctor]
unless rebutted by other competent medical testimony." By fail-
ing to specify what might count as a defense, Mulder leaves the
medical profession, trial courts, and juries with no guide other than
the insert.

Considering several defenses that doctors might raise illustrates
the problems the Mulder court failed to address. First, the defen-
dant might attack the quality of the insert itself as a standard by
testifying that he disregarded an insert recommendation because he
considered all inserts unreliable or because he had reason to be-
lieve the particular recommendation was unreliable. A defense on
the ground that inserts are generally unreliable seems inconsistent
with the presumption of reliability implicit in allowing insert infor-
mation to establish a prima facie standard of care. Yet even such
general attacks on inserts are relevant for a jury evaluating a doc-
tor's choice between an insert recommendation and an action based
on other sources of information. The testimonial risks associated
with insert evidence should discourage too strong a presumption of
reliability, especially since the recommendations most frequently
used by plaintiffs in malpractice actions do not require support from

194 288 Minn. at 340, 181 N.W.2d at 887-88.
195 Id.
text and notes at notes 88, 92 supra. But see text and notes at notes 90-91 supra.
197 See, e.g., Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560,
317 P.2d 170 (1957) (recommended dosage allegedly inadequate to produce desired results).
This defense merges into reliance on alternative sources of information. See text and notes
at notes 201-04 infra.

A defendant might also offer evidence that he did not consider when making his decision.
The status of such evidence raises an interesting problem. Since the sources were not con-
sulted, they should not affect an evaluation of the doctor's method of making his decision.
Yet if they are excluded, the doctor might be punished for using the drug properly. Such
information may be more relevant to the issue of causation than to the standard of care.
well-controlled studies. The best protection against the testimonial risks is to give the defendant an opportunity to impeach a particular recommendation.

A second possible defense is that the doctor's actions conformed to the standard practice of the profession. If compliance with the professional standard is a defense as a matter of law, the Mulder approach would resemble the burden-shifting approach discussed above. Compliance with the professional standard does not exhaust the possible defenses. A doctor might argue that he relied on his own experience, consultation with other doctors, a reference other than the insert, or some other source, or claim that the special circumstances of the case justified departing from the insert. Under the professional standard rule, such defenses would have to be proved to be consistent with the practice of at least a respectable minority of the profession. This requirement will rarely impose a great burden on doctors, who have ready access to expert testimony, and courts concerned primarily with relieving

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198 Indications are the only category requiring such studies. See note 75 supra.
199 Compliance with the professional standard has been recognized as an adequate defense in several cases where courts have considered inserts as "evidence of negligence." See, e.g., Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 317 P.2d 170 (1957); Brune v. Belinkoff, 354 Mass. 102, 235 N.E.2d 793 (1968); Ball v. Mallinkrodt Chem. Works, 53 Tenn. App. 218, 381 S.W.2d 563 (1964); cf. Crouch v. Most, 78 N.M. 406, 452 P.2d 250 (1967) (controversy among medical practitioners over the proper procedure held a good defense). At least one court sent the case to the jury in spite of uncontradicted expert testimony that the defendant's conduct conformed to the standard of practice in the community. See Incollingo v. Ewing, 444 Pa. 263, 282 A.2d 206 (1971).
200 The statement in Mulder that some explanations might be sufficient as a matter of law unless rebutted by competent expert testimony suggests this interpretation. 288 Minn. at 340, 181 N.W.2d at 887. However, the opinion states that the negligence issue will usually go to the jury. Unless the court assumed that doctors will usually be unable to prove compliance with the professional standard (a dubious assumption given the realities of expert testimony), it probably did not intend to make compliance a defense as a matter of law.
202 See Marchese v. Monaco, 52 N.J. Super. 474, 145 A.2d 809 (Super. Ct. App. Div. 1958), cert. denied, 28 N.J. 565, 147 A.2d 609 (1959) (rejecting defense of consultation where defendant had conferred with experts in the relevant field, but had failed to show them the insert or alert them to the dangers the insert revealed).
206 See 1 D. LOUISELL & H. WILLIAMS, supra note 111, ¶ 8.04, at 204 & n.70.
what they perceive as an unfair disadvantage of plaintiffs are unlikely to relax the defendant’s burden.

Another possible defense is that the doctor obtained the plaintiff’s informed consent before deviating from the insert. Courts have recently concentrated on the lack of informed consent as a sword, rather than the presence of informed consent as a shield. But a doctor’s disclosure—whether required or voluntary—that his actions will deviate from an insert recommendation might be introduced as a defense if a patient who consents to such treatment later sues. The hard issue is not whether a patient’s informed consent should constitute a defense, but under what circumstances a patient’s acquiescence can qualify as informed consent. Defining standards for informed consent, a difficult task in the cases expanding causes of action for lack of informed consent, may be especially problematic in prescription drug cases where patient package inserts are involved.

Finally, defendants in cases involving inserts have sometimes claimed that they were ignorant of an insert recommendation, or had been misled by representatives of the drug manufacturers. Claiming ignorance may prove attractive in jurisdictions where treatises cannot be admitted unless the defendant admits that he consulted them and recognizes their authority. But the reasons for this restriction are less applicable to evidence as widely available and as well recognized as inserts. Mere ignorance of an insert’s recommendation should not excuse a doctor from explaining his deviation. Misinformation by a manufacturer’s representative is

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207 See generally id. ¶ 9.03, at 238-46.
208 Recent decisions have challenged a physician’s traditional authority to determine what a patient should be told. See note 6 supra. Courts may soon require doctors to inform their patients when they are deviating from an insert recommendation. Cf. Sharpe v. Pugh, 270 N.C. 598, 155 S.E.2d 108 (1967) (doctor has duty to inform parents of dangers of giving Chloromycetin to child for minor infection); 21 U.S.C. § 355(i) (1970); 21 C.F.R. § 310.102 (1977) (doctor using Investigational New Drug must get patient’s informed consent). But see Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 577, 317 P. 2d 170, 180 (1957) (mere departure from manufacturer’s recommendation is not “experimentation” requiring informed consent “where such departure is customarily followed by physicians of standing in the locality”).
209 See authorities cited note 6 supra.
210 See note 2 supra; cf. Raymond v. Eli Lilly & Co., 412 F. Supp. 1392, 1402 (rejecting defendant drug company’s contention that patient should have been aware of information on possible adverse effects of oral contraceptives that was on the physician’s insert).
more serious since many doctors rely extensively on "detail men" to learn the latest information on prescription drugs. A doctor should be able to look to a drug company for indemnification if he justifiably relies on the representation of the company agent. Although such misrepresentation may be difficult to prove, the innocent patient seems the least equitable candidate for bearing any resulting loss.

D. The Use of Insert Evidence by Defendants

In addition to defending their departures from inserts, doctors may attempt to benefit from the growing recognition of insert evidence by introducing insert information in their defense. While the major uses of insert evidence have reflected the efforts of courts seeking to lighten the burden on plaintiffs under the traditional rules, the possibilities for the defensive use of inserts also require consideration.

Two reasons explain why doctors seldom complain about the restrictive treatment of inserts under present law, even when the insert information supports a doctor's case. First, the professional standard rule and expert testimony requirement favor the side with the best access to experts. Second, in many cases present law will permit doctors to use inserts effectively in defending themselves. If a doctor desires to bring certain insert information before the jury, he can probably reveal it as part of the basis of his own testimony or introduce it to supplement his testimony under the learned treatise exception to the hearsay rule.

Those opposed to expanding the role of inserts as defensive evidence can argue by analogy to customs and statutes as evidence of the standard of care that while "subconformity" with insert recommendations tends to establish negligence, conformity does not establish due care. This argument echoes sentiments currently expressed by doctors criticizing the inadequacies of inserts, and is supported by cases holding that the FDA's approval of an insert does not establish that a drug manufacturer has satisfied his common law duty to warn. However, the language and reasoning of

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215 Joining the doctor and the drug company in the same suit should eliminate the possibility for inconsistent results.
216 See note 105 supra.
217 See text and notes at notes 140-54 supra.
218 See Morris, supra note 164, at 1153-61.
219 See text and notes at notes 88, 92 supra.
220 See, e.g., McEwen v. Ortho Pharmaceutical Corp., 270 Or. 375, 397-98, 528 P.2d 522,
some cases admitting inserts as plaintiff's evidence might also support the defensive use of the documents, and the cautious bias of the FDA may make inserts more reliable as defensive than as offensive evidence.

Plaintiffs might also argue that there is no necessity for doctors to use insert evidence since physicians have access to expert testimony unhampered by the "conspiracy of silence". This argument assumes that experts will be generally available to doctors at low cost, discounts the expense of the resources consumed even when experts "volunteer" their services, and ignores a possible opportunity to weaken the "conspiracy" by making doctors, who are all potential defendants, less dependent on the testimony of their colleagues and therefore perhaps more willing to testify for plaintiffs. Nevertheless, doctors need inserts far less than plaintiffs do, and current law gives doctors a greater opportunity to use them.

A final argument against allowing doctors to rely more heavily on inserts as a defense is that doctors seeking to avoid liability would make prescribing decisions by following "cook-book" directions. This danger is greatest if courts allow inserts to establish the standard of care, an approach not justified for either plaintiffs or defendants. Courts can alleviate the problem by limiting insert evidence to the rules justified by the characteristics of the various categories of information. While this approach will not create significantly different possibilities for the defensive use of inserts than those allowed under current law, the limitations are required by the characteristics of inserts and the policies underlying the traditional rules governing malpractice litigation.

V. THE INSERT AS EVIDENCE OF CAUSATION

Courts have given even less adequate attention to the use of inserts as evidence of causation than to their use as evidence of the standard of care, in spite of the fact that the causation issue may well determine the outcome of a case. The traditional rule re-

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quires a plaintiff to produce expert testimony that the doctor's negligence caused the plaintiff's injury.\footnote{223} This requirement is based on concerns similar to those supporting the requirement of expert testimony on the standard of care: the need for expert assistance on complex scientific issues and the fear that immaterial considerations may affect a jury's decision.\footnote{224} As courts have relaxed the requirements for proving the standard of care, the causation issue has become more important to defendants as a means of keeping a case from the jury. Some decisions that allow inserts a prominent role in determining the standard of care continue to require expert testimony on the causation issue, even when an insert warns that the alleged misuse of the drug can lead to the particular injury suffered by a plaintiff.\footnote{225} Other courts seem less rigorous in their demand for proof of causation,\footnote{226} but no court has specifically discussed the use of inserts as evidence of causation.

The courts' relative reluctance to loosen the requirement for expert testimony on causation is surprising since a major justification for requiring expert testimony on the standard of care—the desire to protect a doctor's independent judgment—is much weaker in the context of causation. On the other hand, insert information may be less useful on causation issues than on the standard of care. Controversies over causation arise when there are multiple possible causes for a particular injury, a frequent phenomenon in medical malpractice trials.\footnote{227} An alleged injury might be caused by a combination of factors including the patient's disease, the nonnegligent use of a drug, the patient's hypersensitivity, an inadequate disclosure of risks by the manufacturer or doctor, or the doctor's negligence in diagnosis or in choice or administration of treatment. Insert information indicates only whether the use of a particular drug is a

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\textsuperscript{222} See 1 D. Louisell & H. Williams, supra note 111, ¶ 11.20, at 324-27; Annot., 13 A.L.R. 2d 11, 31-34 (1950).

\textsuperscript{223} Expert testimony may not be required if the causation question is within the expertise of laymen. Annot., 13 A.L.R. 2d 11, 34-36.


\textsuperscript{226} See, e.g., id.; Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 317 P. 2d 170 (1957); Lhotka v. Larson, 238 N.W. 2d 870, 875 & n.18 (Minn. 1976); 1 D. Louisell & H. Williams, supra note 111, ¶ 8.07, at 213-17.
possible cause of an injury and does not weigh the various possibilities to determine the most probable cause (or even the proximate causes) under given circumstances. In most multiple causation cases, the problem is the amount of evidence the plaintiff must produce to take the causation issue to the jury. In determining the weight to be given insert information, courts should evaluate the relevance and reliability of the particular information involved. If the use of a given drug is the alleged negligence, information that the drug is associated with the type of injury suffered by the plaintiff is relevant evidence of causation. If the method of administering an admittedly proper drug is attacked, the insert information should tie the injury to the negligent act rather than to the use of the drug in general. For example, the injury might be listed as a possible consequence of overdosage or as a reaction that would have been predicted by sensitivity tests, rather than as a mere adverse reaction.

The reliability of various categories of insert information as evidence of causation is suggested by the proposed regulations. Adverse reactions must appear if "reasonably associated with the use of the drug," even if reactions have been reported only in connection with drugs "of the same chemical or pharmacological class." Information on the probability of particular adverse reactions (if given) must indicate the level of support behind the "reasonable association." Warnings are to be included "as soon as there is reasonable evidence of an association of a serious hazard with a drug: a causal relationship need not have been proved." "Known hazards and not theoretical possibilities" are to be listed as contradictions. In spite of the generally low threshold requirements for adding limiting information, many statements in these categories have substantial support, and acquiring better evidence on causation—even from experts—is usually difficult.

The impact of inserts as evidence of causation may depend more on how a court defines the burden of proof in multiple cause cases than on the weight assigned the insert. The general rule is that the plaintiff must prove a reasonable probability, not just a possibility, that his injury resulted from the defendant's negligence; the

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228 See note 75 supra. The usefulness of the various categories of information as evidence of causation is hampered because the standards for including information reflect the seriousness of reactions more than their probability.

jury is not allowed to "speculate" among equally probable causes. Nevertheless, at least one case where an insert was used as the standard of care has suggested that a jury should be given wide discretion to choose among several possible causes. Whatever standard is adopted, relevant and reliable insert evidence—at least contraindications, warnings, and adverse reactions based on clinical studies rather than random reports—should be considered by the judge and jury in making their respective decisions.

Defendants as well as plaintiffs might introduce insert evidence on the causation issue. A defendant can claim that the reactions not listed on the insert are probably not caused by the drug, or use insert information to prove that the patient's injury could have occurred even if the drug had been used properly. Where inserts are used as evidence of causation rather than the standard of care, a court cannot differentiate between offensive and defensive uses by holding that the insert establishes a subminimum standard. The low thresholds of support that are sufficient to connect a drug with an adverse reaction and the emphasis on collecting adverse reaction reports may make evidence more reliable on the defensive than on the offensive side.

CONCLUSION

In response to the difficulties created for plaintiffs in medical malpractice trials by the traditional professional standard of care rule and expert testimony requirement, courts have begun to admit as evidence information from package inserts prepared by drug manufacturers according to FDA regulations. Although insert evidence is technically hearsay if used to prove the standard of care or causation, the guarantees of reliability built into the insert preparation process and the difficulty of acquiring more reliable evidence justify admitting insert statements under an exception to the hearsay rule. The relevance and significance of insert evidence depend on whether and how courts use insert evidence to modify the traditional definition of the standard of care and the burdens of proof.

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232 In Nolan v. Dillon, 261 Md. 516, 536-37, 276 A.2d 36, 47 (1971), the court, adhering to a conservative rule on the admissibility of medical treatises, excluded medical articles introduced for this purpose.
233 See text and note at note 218 supra.
234 See note 75 supra. The evidence is still questionable, however. A manufacturer may fear that adding such information would discourage sales or encourage product liability suits.
Insert statements can be used as evidence of the standard of care without threatening the policies protected by the traditional rules if courts distinguish among the categories of insert information and allow a statement as independent evidence of the standard of care only if it comes from a category requiring reliable support and makes a clear recommendation on a question that can be settled without the need for an attending doctor's judgment. Most insert information is designed to provide data necessary for doctors to make informed judgments in particular cases and is inadequate by itself to establish the standard of care. Insert information is also relevant to the causation issue, but here again inserts provide data rather than weighing alternative possibilities and suggesting an answer. Inserts cannot solve the dilemma created by the desire to protect both the doctor's independent judgment and the patient's right to nonnegligent treatment. But if their limitations are recognized and respected, inserts can provide informative evidence that will help courts and juries reach results that minimize the inherent conflict between these two goals.

James R. Bird
WARNING
Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the “Indications” section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

DESCRIPTION
Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see “Indications” section).

ACTIONS AND PHARMACOLOGY
In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active in vitro against rickettsias, the lymphogranuloma-psittacosis group and Vibrio cholerae. It is particularly active against Salmonella typhi and Hemophilus influenzae. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8–14 mcg./ml. over the
CHLOROMYCETIN
(CHLORAMPHENICOL)

48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS
IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDIATED. HOWEVER, CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; IN VITRO SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY IN VITRO STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. Acute infections caused by Salmonella typhi

Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state."

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:
   a. Salmonella species

*In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.
b. *H. influenzae*, specifically meningeal infections

c. *Rickettsia*

d. Lymphogranuloma-psittacosis group

e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections

f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. Cystic fibrosis regimens

**CONTRAINDICATIONS**

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.

**PRECAUTIONS**

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.
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ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3 month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:
In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.

Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.

The symptoms appeared in the following order:
(a) abdominal distension with or without emesis;
(b) progressive pallid cyanosis;
(c) vasomotor collapse, frequently accompanied by irregular respiration;
(d) death within a few hours of onset of these symptoms.

The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).

Termination of therapy upon early evidence of the associated symptomaticology frequently reversed the process with complete recovery.

**DOSAGE AND ADMINISTRATION**

**DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS**

The majority of microorganisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over most of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will usually achieve and sustain levels of this magnitude.

Except in certain circumstances (e.g., premature and newborn infants and individuals with impairment of hepatic or renal function) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Close observation of the patient should be maintained and in the event of any adverse reactions, dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

**Adults**

Adults should receive 50 mg./kg./day (approximately one 250 mg. capsule per each 10 lbs. body weight) in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

**Children**

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon
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as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants
(See section titled "Gray Syndrome" under "Adverse Reactions.")
A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes
In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

PACKAGE INFORMATION
Kapseals No. 379, Chloromycetin (chloramphenicol capsules), each contain 250 mg. chloramphenicol, supplied in packages of 16 and 100, and Roll-Pak* of 100.
Capsules No. 477, Chloromycetin (chloramphenicol capsules), each contain 50 mg. chloramphenicol, supplied in packages of 25 and 100.
Capsules No. 480, Chloromycetin (chloramphenicol capsules), each contain 100 mg. chloramphenicol, supplied in packages of 25 and 100.


*Trademark for dispensing package

PARKE, DAVIS & COMPANY
121 852800

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