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Accutane and the evolution of a warning

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Informed consent is a well-established doctrine in the field of medical liability law. The duty to obtain informed consent stems from the principle that a patient should have information that is necessary to deciding upon a course of treatment. For a long time, the unpredictabilities of medical science impeded the acquisition of proper informed consent [1]. The last century, though, has seen a tremendous increase in the ability of physicians to anticipate most or all of the risks associated with a given treatment or procedure.

The requirement that physicians obtain informed consent prior to treatment now extends to the dispensing of pharmaceuticals because of the wide-ranging side effects that many drugs have been found to exhibit. The responsibility to warn patients of risks rests with the prescribing physician rather than with the manufacturer of the drug; the manufacturer has the responsibility to provide the physician with appropriate information [2]. A physician who fails to warn a patient or a manufacturer who fails to warn physicians of risks associated with a particular drug may incur liability for that error.

Accusations that the duty to obtain informed consent was not fulfilled have resulted in far-reaching efforts to strengthen the informed consent process. Such allegations concerning the prescription acne medication Accutane (known generically as isotretinoin) triggered an evolution in the warning provided to patients about the drug.

When Accutane was first released, its manufacturer strongly suspected that it could cause birth defects if women took it while pregnant or at the time of conception. Hoffman-LaRoche, the drug's manufacturer, maintained that it had no solid evidence in human subjects but that teratogenicity had been observed in rats. The warning provided to patients in 1982 noted this fact, instructed patients to use an effective form of contraception while on Accutane and recommended the use of contraception for one month after discontinuation of the therapy [3]. Accutane was also labeled as a "Category X" drug, meaning that it should not be used while a woman was pregnant. The 1982 warning was sufficient to inform users of the dangers and to aid the manufacturer in avoiding liability, according to the Florida Supreme Court.

Even though the 1982 warning was sufficient at the time, later reports of abnormalities of human fetuses prompted a change that made the warning more stern [4]. While many of the recommendations remained essentially the same, the new warnings listed each of them in a separate paragraph to improve clarity. In subsequent cases, courts again held that the warnings were sufficient, noting that they provided enough information to inform the plaintiffs of the harms they ultimately experienced.

Perhaps because of the frequency of lawsuits over Accutane and the claims that the patient-plaintiff had not been fully informed by the physician or that the patient-plaintiff had not been cautioned about the possibility of contraceptive failure, the warning provided prior to initiating Accutane therapy was changed again. By 1995, it had become more explicit, and patients were required to initial each paragraph in the warning to show that they had read it [5]. Because of the required initials, patients were no longer able to claim that the physician failed to inform them of the risks associated with Accutane. The warning included more detailed information on the requirement to use birth control—including a statement that any form of birth control can fail—and required patients to state that they were not pregnant and would not become pregnant for at least 30 days after completing Accutane therapy.

This did not prevent a patient from filing a lawsuit against Hoffman-LaRoche claiming its failure to sufficiently warn was the cause of her child's abnormalities. Most interestingly, *Banner v Hoffman-LaRoche* was based upon the failure of abstinence and the failure to warn of the possibility that this method of contraception was unlikely to be successful in certain circumstances. The court noted in this case that the manufacturer should not be held liable for failure to warn of a risk already known, i.e., that having sexual intercourse would make abstinence ineffective as a form of contraception.

Lawsuits continued to be filed, and the informed consent requirement and the warning about the effects of Accutane have become more explicit and rigid. In March of 2006, the iPLEDGE program was instituted to further reduce the incidence of birth defects caused by Accutane (as well as further solidify the legal ground of physicians and manufacturers of isotretinoin). Participation in the program is required for both female and male patients, as well as physicians and pharmacists [6]. Patients must also sign Patient Information/Informed Consent forms and to agree to follow program steps.

In addition to providing even more detailed information to patients than previous warnings, iPLEDGE introduces strict requirements for obtaining Accutane. A patient must agree to use two forms of contraception—and provide proof of use. The program specifies primary and secondary forms of contraception. Female patients must take a pregnancy test in order to obtain the medication and before receiving each prescription refill. Participation in the program is mandatory for all parties in the process: patient, physician, pharmacist, pharmaceutical wholesaler and

manufacturer. The purpose of the program is to ensure, with more certainty than ever, that a woman will not become pregnant while taking Accutane.

In sum, there has been a clear pattern of change in the warning accompanying Accutane over the past two decades. As lawsuits progressed, even without success, warning mechanisms evolved to meet many of the legal complaints. As the responsible government agency, the FDA had oversight of postmarket problems throughout this period, and in 2004 its advisory committee recommended more stringent regulation [7]. While the first warning had been very general, merely informing of the possible effects and recommending contraception, informed consent requirements were gradually strengthened, eventually obligating patients to sign their initials as proof of a proper warning. The need for two forms of contraception became explicit, and a statement of the possibility that contraception can fail was added. With the introduction in 2006 of the iPLEDGE registry program, agreed upon by FDA and industry, contraception and pregnancy tests are prerequisites for each one-month prescription. The possibility of the failure of contraceptive methods—abstinence included—is incorporated into the informed consent process for Accutane.

Informed consent is both a legal and an ethical requirement. Both share the intent that patients make informed decisions regarding treatment, but demands that satisfy the legal standard may not always satisfy the ethical standard. Hence, in the case of Accutane, although the courts found that the 1982 warnings satisfied the legal requirements, sensitivity to ethical standards prompted further revisions to the recommendations for informed consent. Moreover, it is apparent from the Accutane experience that patients do not always understand what they are told or may, in hindsight, feel as though their decision was not based on all appropriate information. The evolution of the warning provided to Accutane patients illustrates how continuing concerns brought about by legal battles can lead to a new understanding of what exactly “informed consent” is.

References

1. See generally, *Salgo v Leland Stanford Jr. University Board of Trustees*, 317 P2d 170 (Cal Ct App 1957).
2. *Cunningham v Pfizer*, 532 P2d 1377, 1381 (Okla 1974).
3. *Felix v Hoffman-LaRoche*, 540 So2d 102 (Fla 1989).
4. *Gerber v Hoffman-LaRoche*, 392 FSupp 2d 907 (SD Tex 2005); *Bealer v Hoffman-LaRoche*, 729 FSupp 43 (ED La 1990).
5. *Banner v. Hoffman-LaRoche*, 891 A2d 1229 (NJ App 2006).
6. iPledge. *iPledge home page*. Available at: <https://www.ipledgeprogram.com/>. Accessed June 27, 2006.
7. Harris G. FDA imposes tougher rules for acne drug. *New York Times*. August 13, 2005. Available at <http://www.nytimes.com/2005/08/13/health/13fda.html?ex=1151640000&en=57a8421697df44e3&ei=5070>. Accessed June 28, 2006. See also Food and Drug Administration. *Letter from Florence Houn, MD, Director, Office of Drug*

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