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Editorial

The “FDA approval defense”: penetrating the protective shield

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Pharmaceutical manufacturers decry the purported burdens imposed by Federal regulation when it suits their proprietary interests, yet they sing a wholly different tune when defending product liability suits. As product liability defendants, they unabashedly seek the protective womb of Food and Drug Administration (FDA) regulation, arguing that agency approval of their drug and its labeling precludes their product from being regarded as defective or their conduct characterized as tortious.

Several states have recognized FDA approval as a defense in product liability actions for certain purposes. Most notably, a number of states exempt pharmaceutical manufacturers from liability for punitive damages arising from use of any drug approved by FDA [1]. A similar exemption has been incorporated in a number of Federal tort reform bills that have been introduced over the past several years in Congress [2].

Most courts have rejected pharmaceutical manufacturers’ argument that compliance with FDA regulatory requirements preempts a finding of liability for negligence, defective design, and inadequate warnings under state tort law. FDA regulation of prescription drugs is “generally viewed as setting minimum standards, both as to design and warning” [3]. Compliance with FDA regulatory requirements is not dispositive on the design and warning issues if it were reasonable to have done more [4].

Even where courts have rejected Federal preemption as a defense to a pharmaceutical product liability suit, a drug company defendant will not hesitate to urge deference to the purportedly pre-eminent expertise and knowledge of FDA [5], the agency that previously determined that the drug’s benefits outweighed its risks and justified its marketing and approved the warnings, precautions, contraindications, and other safety-related information contained in the drug’s labeling [6]. Pharma-

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ceutical company defendants commonly maintain that they have met or exceeded all applicable FDA requirements and have not materially deviated from any regulation, statute or guidelines to which they were subject, all of which evidence that they were not negligent and their drug is not defective. Courts that do not honor the preemption defense nonetheless frequently accommodate drug makers by permitting the trier of fact to take their alleged compliance with the government standards of FDA into account [7]. FDA approval may be accorded whatever weight the trier of fact determines that it deserves [8] and may be disregarded where the jury sees fit [8a]. Even FDA's regulations, however, recognize that, in the area of drug labeling, agency approval does not automatically relieve manufacturers of the duty to include, where appropriate, additional warning, precautionary or side effect information in such labeling. In this connection, FDA regulations since 1965 have permitted manufacturers to effect certain safety-enhancing changes in new drug labeling without prior authorization from FDA [9].

FDA approval may also be unavailable as a defense where a defendant manufacturer failed to report or otherwise misrepresented to FDA important adverse drug safety information in its possession, custody, or control, such circumstance resulting in the misbranding, if not the improper marketing, of the drug in question [10]. FDA cannot responsibly and intelligently assess the risks of a drug if it is deprived of critical information regarding them [11]. Notably, states which have prohibited punitive damages arising from use of drugs approved by FDA have repeatedly permitted their award where it has been shown that the drug company defendant withheld material drug safety information from FDA [12]. Federal "product liability reform" legislation also denies an FDA approval defense to punitive damages for drug industry defendants who have committed fraud during the pre-approval review process by withholding from or misrepresenting to FDA information that is material and relevant to the performance of that drug [13].

Implicit in the "FDA approval defense" is the assumption that FDA regulation adequately protects the public from the dangers of marketed drugs [14]. Congressional oversight of FDA's performance, however, is littered with numerous instances challenging the validity of this assumption. To be certain, shortly after enactment of the Drug Amendments of 1962, which substantially overhauled the nation's drug regulatory laws, and continuing into recent times, egregious shortcomings in FDA's regulation of the safety of new drugs have been repeatedly exposed. It behooves the plaintiff's attorney, where a drug company has opened the door on FDA's regulatory performance by arguing that it has complied with the purportedly rigorous government standards created and enforced by FDA, to be knowledgeable of instances in which serious deficiencies in FDA's approval of drugs and drug labeling and monitoring of drug safety have been documented.

Inadequate pre-market safety review

FDA has not always been knowledgeable, prior to approving new drugs for marketing, of available and highly significant adverse safety information associated

with their use, even when such information resides in its own files. Witness the case of the anti-arthritis drug Oraflex (benoxaprofen), which was withdrawn by its manufacturer, Eli Lilly & Company, a few months after it was approved in 1982 because of a large number of serious and sometimes fatal liver and kidney reactions associated with its use. FDA was wholly unaware of four Oraflex clinical trial reports of serious Oraflex-associated liver reactions — including hepatitis and jaundice — that Lilly had submitted to FDA’s investigational new drug (IND) file for the drug prior to FDA approval, because of a filing backlog in the documents room of the division responsible for reviewing the safety of the drug [15]. In reviewing this unfortunate sequence of events, the House Committee on Government Operations later concluded that “[h]ad such reports been noted, it is unlikely that FDA would have originally approved labeling for the drug which made no mention of liver disease and which confined Oraflex-associated liver reactions to ‘liver function test abnormalities’ which were ‘usually transient’” [16]. The committee also found that Lilly had prominently reported to the Oraflex IND a total of six cases of drug-associated kidney disease prior to the drug’s approval [17]. Yet, Lilly proposed, and FDA approved, labeling which flatly denied any “evidence... of renal toxicity in the clinical studies” [18]. Moreover, as of a congressional hearing on August 3, 1982 — three and one-half months after Oraflex was approved — FDA still was unable to confirm the manufacturer’s assertion that it had reported serious drug-associated adverse effects to the agency prior to the drug’s approval [19].

FDA also did not know more than five months after approving Oraflex and seven weeks following the drug’s market withdrawal whether Lilly had reported to it any Oraflex-associated deaths before approval, a circumstance which, the House Committee on Government Operations concluded, signalled that “the agency had not thoroughly examined the sponsor’s IND and NDA submissions before approving the drug for marketing” [20].

Such glaring omissions besetting the agency’s discharge of its statutory responsibilities have a long lineage. Premonitions of the Oraflex experience surfaced more than two decades earlier with McNeil Laboratories’ new drug Flexin (zoxazolamine). FDA approved Flexin on January 13, 1956, for the relief of muscle spasm in conditions such as musculo-skeletal disorders and neurological diseases [21]. On October 13, 1961, FDA suspended the Flexin new drug application (NDA), after receiving a large number of reports of hepatitis, including deaths, associated with its use [22]. As with Oraflex more than two decades later, FDA officials were found to be totally unaware of the drug’s association with hepatitis and jaundice during much of its marketing. Lilly’s failure to report serious and sometimes fatal liver reactions associated with use of Oraflex outside the United States contributed to FDA’s assumption, when it approved the drug, that Oraflex had not been implicated in the onset of hepatitis and jaundice [23]. While FDA’s ignorance of Flexin-associated hepatitis and jaundice was similarly attributable, in part, to McNeil’s failure to apprise the agency of all reports received of adverse liver reactions to Flexin [24], the agency conceded, as it was forced to do years later with Oraflex, that it had completely overlooked several such reports retained in its own

files that had been submitted to it by its manufacturer. For example, the agency neglected to note the manufacturer's acknowledgment in June 1958 of "occasional reports of patients who have developed jaundice" [25]. FDA also overlooked a statement included in a supplemental NDA submitted for a Flexin-containing drug on September 29, 1958, that "during the past 3 1/2 years there had been a total of 32 reports to McNeil suggesting that the administration of the drug [Flexin] may have been associated with development of hepatitis with jaundice" [26]. Then FDA Commissioner George P. Larrick admitted in congressional testimony that this information "did suggest strongly the relationship between drug-induced hepatitis and the drug, came to the new drug branch and had not been reviewed" [27]. Accordingly, three medical officers indicated in writing that they were not aware that Flexin had potentially induced hepatitis [28]. Ironically, as if to foreshadow the Oraflex episode of a later era, FDA's failure to consider reports of drug-associated liver injury was ascribed to a failure to examine documents comprising a backlog of unreviewed submissions received from regulated manufacturers [29].

That the Oraflex experience so strongly resonates with echoes from the agency's regulation of Flexin is particularly ironic in that these drugs shared a highly unusual property; they comprised two of only three drugs ever approved by FDA that prominently featured a particular structure as part of their chemical or molecular composition [30]. In fact, the House Committee on Government Operations concluded that "Oraflex's chemical similarity to Flexin... should have alerted FDA to its potential liver toxicity" [31]. The Flexin and Oraflex sagas dramatically underscore the enduring truth of Santayana's admonition that those who ignore history are condemned to repeat it.

In the wake of revelations regarding deficiencies in FDA's pre-approval review of the safety of Oraflex, Congress chronicled additional oversights marring the agency's pre-market assessment of the hazards of the nonsteroidal anti-inflammatory drug Zomax (zomepirac sodium). Although the originally approved Zomax labeling did not mention the drug's reported association with allergic/anaphylactoid reactions, a congressional committee found that FDA had received but failed to notice clinical trial reports of such reactions prior to approving the drug [32].

FDA was also found to be unfamiliar with important data it had received from the manufacturer of Versed (midazolam hydrochloride), a drug approved to induce conscious sedation, that suggested that the doses it originally approved for the drug were excessive. That data showed that the drug could effectively produce conscious sedation at levels substantially below these doses [33]. The tragedy resulting from this oversight was manifest. Until FDA required the manufacturer to reduce the dosage levels of Versed many months *after* its approval, a number of reports of serious and sometimes fatal respiratory depression and cardio-respiratory arrest were received, episodes which the agency attributed to an originally approved and recommended dose that was "too high" [34].

Medical illiteracy

In clinical pharmacology, the published medical literature is universally recognized as the most basic and readily accessible repository of information regarding the safety of new drugs. Despite the fundamentally central position which this literature occupies in the universe of existing knowledge concerning new drug safety, FDA has repeatedly been shown to be wholly unaware of important aspects of the toxicity of new pharmacological agents delineated in medical publications. For example, congressional hearings conducted as early as 1964 exposed FDA's lack of knowledge of important information linking the use of the contrast medium, Orabiles (bunamiodyl sodium), to renal failure [35]. In a similar vein, FDA was revealed to lack familiarity with important papers in the world literature published prior to the approval of the antidepressant Merital (nomifensine maleate) that addressed the drug's safety and in particular suggested its toxicity to the human immune system [36].

The Versed case is also exemplary. FDA approved conscious sedation doses of Versed of 0.1 to 0.15 mg/kg and, if necessary, up to 0.2 mg/kg [37]. The House Government Operations Committee found that, prior to approving Versed for use at these doses, the agency was not aware of a number of studies published in prominent medical journals which demonstrated these doses to be excessive [38]. The agency was equally unfamiliar with published studies indicating the efficacy of Versed at conscious sedation doses substantially below those at which it had originally been approved [39]. In originally approving conscious sedation doses for Versed that were comparable to those that it had approved and which were then being recommended for intravenous Valium (diazepam), FDA was not aware of a Swedish study published prior to its approval of Versed strongly suggesting that Versed was three times as potent as Valium when used intravenously as an anesthetic. Therefore, Versed should have been approved for use at substantially lower conscious sedation doses than those recommended for Valium [40]. Incredibly, as late as a House hearing on May 10, 1988, almost two and one-half years after FDA had approved Versed for marketing, agency regulators of the drug still were not aware of the existence of this study [41].

Legally questionable approval of unsafe drugs

A product liability suit cannot serve as a forum for adjudicating the legality of FDA's decision-making. However, if faced with claims that FDA only approves drugs where clinical evidence complies with all applicable legal requirements, plaintiff's counsel may want to call to the court's attention that FDA has endangered the health and safety of patients by the approval of drugs which, by FDA's own account, had not been shown safe within the meaning of the premarket approval requirements of the law. The history of Triazure (azarabine) is illustrative. FDA approved Triazure for the treatment of psoriasis on February 28, 1975. In August 1976, approximately one year after the drug was introduced to the

market, FDA issued a press release warning patients taking Triazure immediately to discontinue its use, because of its capacity to produce fatal blood clots in veins and arteries [42].

FDA not only recognized the propensity of Triazure to produce serious blood clots prior to approval but, in fact, had determined that, in light of this risk, the law required it to disapprove the Triazure new drug application unless additional testing were completed that illuminated the risk of drug-induced blood clotting. Accordingly, by letter dated June 26, 1973, FDA advised the manufacturer that

the [new drug] application is inadequate under section 505(b)(1) of the Act in that there is insufficient clinical evidence on which a judgment can be made that the benefits of the drug outweigh the risks. Adequate clinical testing by all methods reasonably applicable to show whether or not the drug is safe for use as recommended in the proposed labeling, is lacking. The thromboembolic phenomena as reported in the well-controlled study, is considered a definite drug related event. We have concluded that *further testing is necessary* in order to define more clearly the degree of risk of thromboembolism in psoriatics treated with Triazure [43]. (Emphasis supplied)

In the face of the manufacturer's refusal to conduct such additional pre-market testing, FDA subsequently approved Triazure anyway, notwithstanding its prior conclusion that, without such testing, clinical evidence of the type required by §505 of the Food, Drug, and Cosmetic Act [44] was lacking to support any conclusion that the drug's benefits outweighed its risks. By the agency's own reckoning, Triazure was marketed prior to its being shown safe for its intended use. The results of such premature commercialization were tragic. When Triazure was removed from the market, it had been linked to serious injury and even death in patients from blood-clotting [45].

Deficient post-market monitoring of drug safety

FDA's lack of awareness of important data bearing on the safety of new drugs languishing in its own files is not confined to pre-market reports of adverse effects. The case of Versed is again exemplary. Important information revealing Versed to be far more likely to oversedate patients and thus expose them to a serious risk of respiratory depression than injectable Valium was discernible from data included in a clinical trial report submitted to the agency on September 26, 1986, nine months after agency approval of Versed [46]. That FDA is not always aware of this and other potentially important safety data may sometimes simply reflect limitations on its already overworked and understaffed personnel to examine and assess the inordinate volume of paperwork it continuously receives from the regulated industry. Thus, "[b]uried as it was in a voluminous" submission made after FDA approval to the Versed IND file, a congressional committee observed of the September 1986 report that it "not surprisingly, apparently went unreviewed by FDA" [47].

Although FDA requires that certain post-market reports of drug-associated adverse reactions be timely submitted to it [48], the agency has been publicly exposed as uninformed of large numbers of such reports that have been forwarded to it. For example, an FDA employee testified at a 1983 congressional hearing that he was surprised when McNeil Pharmaceutical, the manufacturer of Zomax, informed FDA at a February 11, 1983, meeting that it had submitted to FDA 908 reports of allergic/anaphylactoid reactions associated with the drug's use since its approval. An FDA memorandum of a February 28, 1983, meeting with McNeil indicated that shortly before the drug was withdrawn from the market, the agency's computerized tracking system contained 270 reports of Zomax-associated allergic/anaphylactoid reactions [49].

These revelations only confirmed what had earlier been found by the General Accounting Office (GAO). In a March 8, 1982, report entitled, *FDA Can Further Improve Its Adverse Drug Reaction Reporting System*, GAO found that FDA's Division of Drug Experience — the agency unit then responsible for tracking post-market reports of drug-associated adverse effects — took an average of 3.3 months and sometimes more than a year to enter such reports into its computerized monitoring system [50]. Prior to the market withdrawal of Zomax, Congress found that FDA also failed to analyze data in its possession strongly intimating that Zomax was associated with a higher incidence of anaphylactoid reactions than other drugs in its class [51].

Following what it thought was a temporary suspension of the marketing of Zomax, McNeil proposed remarketing the drug with labeling emphasizing that a "majority" of life-threatening and fatal anaphylactic reactions reported for the drug occurred in "individuals without a prior allergic history" [52]. That such reactions could unpredictably and unforeseeably strike users without an allergic drug history clearly heightened the drug's dangers [53]. Congressional investigators found that while Zomax was still being marketed, FDA neglected to analyze data it had collected suggesting that this patient group was, indeed, at highest risk of such reactions [54]. As a consequence of this omission, FDA permitted McNeil, prior to the drug's removal from the market, to drop a warning that the company had proposed adding to the Zomax package insert regarding the risk of drug-induced anaphylactoid reaction confronting patients who had previously manifested no allergic reactions to Zomax or other drugs in its class [55]. Noteworthy since the Zomax experience is the GAO's conclusion, based on a review of the "discovery" of serious drug-induced risks associated with the use of new drugs following their approval, that FDA's review procedures may be inadequate to the task of identifying such risks prior to their approval. In its April 1990 report entitled, *FDA Drug Review: Postapproval Risks 1976–85* [56], GAO found that of the 198 drugs approved by FDA between 1976 and 1985 for which data were available, 102 (51.5%) had serious postapproval risks, as evidenced by labeling changes [57] or withdrawal from the market. GAO implied in its recommendations that some serious risks "discovered" subsequent to drug approval, through improvements in the drug review process, might have been identified and addressed during FDA's pre-market review process [58].

Conclusion

In one case, a defendant argued that FDA certification of its vaccine should conclusively evidence “non-negligence per se”. The court rejected this argument, declaring that

FDA certification represents only the FDA’s opinion, albeit an informed one, of the safety and efficacy of the drug. Regrettably, drugs occasionally prove not so safe as the FDA first believed [59].

Accordingly, the court held that “FDA certification of a drug is evidence but not conclusive evidence of the drug manufacturer’s reasonableness; the trier of fact may assign FDA approval the weight it deserves” [60].

That a drug eventually shows itself as clearly more hazardous than FDA knew or assumed, may sometimes be explained, not by the emergence of its truly unforeseeable dark side, but rather by the agency’s inattention or lack of knowledge occasioned by limitations or deficiencies in its scientific review practices and procedures.

With the virtually unlimited resources of large pharmaceutical concerns with longstanding experience with and expertise in FDA regulation of new drugs at its disposal, defendant’s counsel is well-positioned to argue, be it in pre-trial motions or at trial, that the painstaking processes to which FDA subjects manufacturers before approving their drugs forecloses a finding that a defective product has been marketed or that the drug maker has otherwise engaged in actionable conduct. In addition to citing authority that FDA approval only constitutes compliance with minimum standards which do not pre-empt liability otherwise accruing under state tort law, plaintiff’s counsel should also attempt to introduce or rely upon numerous well-documented case histories exemplifying shortcomings in FDA’s review process that have manifestly placed the health, safety, and even the lives of unwitting patients at risk if the defendant opens the door at trial with evidence of its compliance with the allegedly exacting government standards of FDA.

Notes and references

- 1 *See*, for example, Utah Code Ann. §§78-18-2(a) (Supp. 1990); Ariz. Rev. Stat. §12-701(A); N.J. Stat. §2A:58C-5(c); Oh. Rev. Code Ann. §2307.80(C); Or. Rev. Stat. §30.927; Colo. Rev. Stat. §13-64-302.5(5). New Jersey further provides a rebuttable presumption that an FDA-approved warning was adequate. N.J. Stat. §2A: 58C-4.
- 2 Significant efforts to enact so-called product liability reform legislation began in 1983 when S44 was introduced in the 98th Congress. In March 1983, S687 was introduced in the 103rd Congress.
- 3 *Graham v. Wyeth Laboratories*, 666 F.Supp. 1483, 1491 (D.Kan. 1987). *See also* *MacDonald v. Ortho Pharmaceutical Corp.*, 394 Mass. 131, 475 N.E.2d 65 (1985); *Abbot v. American Cyanamid*, 844 F.2d 1108, 1110 (4th Cir. 1988); *Tobin v. Astra Pharmaceutical Products, Inc.*, 993 F.2d 528 (6th Cir. 1993); *Hoppe v. G.D. Searle & Co.*, 779 F.Supp. 1413 (S.D.N.Y. 1991); *Mazur v. Merck & Co., Inc.* 742 F.Supp. 239 (E.D.Pa. 1990); *MacGillivray v. Lederle Laboratories*, 667 F.Supp. 743 (D.N.M. 1987); *Barson v. E.R. Squibb & Sons, Inc.*, 682 P.2d 832, 836 (Utah 1984);

- Ferrigno v. Eli Lilly & Co., 175 N.J. Super. 551, 420 A.2d 1305 (1980); Bristol-Myers v. Gonzales, 548 S.W.2d 416 (Tex. Civ. App. 1976); McEwen v. Ortho Pharmaceutical Corp., 170 Or. 375, 528 P.2d 522 (1974); Stevens v. Parke-Davis and Co., 9 Cal.3d 51, 107 Cal. Rptr. 45, 53, 507 P.2d 653, 661 (1973); and Pollard v. Ashby, 793 S.W.2d 394 (Mo.App. 1990).
- 4 O’Gilvie v. International Playtex, Inc., 821 F.2d 1438, 1442-3 (10th Cir. 1987). Compliance with FDA regulations also “does not preclude punitive damages when there is evidence sufficient to support a finding of reckless indifference to consumer safety.” *Id.* at 1446.
 - 5 Some commentators argue that “[o]nly the FDA is qualified to evaluate the data and make the requisite policy judgments involved in drug regulation.” *See* Landen, Federal Preemption and the Drug Industry: Can Courts Co-Regulate?, 43 Food Drug Cosm. L.J. 85, 117 (1988).
 - 6 Pharmaceutical manufacturers will often advocate similar deference in urging upon courts an interpretation of Comment k to §402A of the Restatement (Second) of Torts which, when adopted by a particular jurisdiction and deemed applicable to a particular case, confers immunity from strict liability upon products regarded as “unavoidably unsafe” within its terms. Comment k shields certain prescription drugs from strict liability which “in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use, so long as they are “properly prepared and marketed, and proper warning is given...” States have generally adopted Comment k, some making it applicable to prescription drugs on a case-by-case basis, others applying it to all prescription drugs as a matter of law. Pharmaceutical company defendants will typically argue that permitting a jury to determine whether a drug is “unavoidably unsafe” is to render it responsible for deciding whether it should be available in the United States. Such a determination, they maintain, requires a regulatory judgment for which FDA alone is qualified and has been delegated the authority to make.
 - 7 Thus, for example, one court has held that “compliance with FDA requirements, though admissible to demonstrate lack of negligence, is not conclusive on this issue, just as violation of FDA requirements is evidence, but not conclusive evidence, of negligence.” *MacDonald v. Ortho Pharmaceutical Corp.*, 394 Mass. 131, 475 N.E.2d 65, 70–71(1985). In a similar vein, another court has stated: “Evidence that the drug was marketed pursuant to FDA approval after submission of test results may be considered by the jury on the issue of whether proper care in general, and adequate testing in particular, were exercised, but it is in no way binding on the fact-finders.” *Ferrigno v. Eli Lilly & Co.*, *supra*, at 1320. *Also see* *Salmon v. Parke-Davis and Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975).
 - 8 *Graham v. Wyeth Laboratories*, *supra*, at 1491.
 - 8a *Tobin v. Astra Pharmaceutical Products, Inc.*, *supra*.
 - 9 *See* 30 Fed. Reg. 993-4 (January 30, 1965), which set forth Section 130.9(d)(1) of FDA’s regulations governing supplemental new drug applications, which stated that labeling changes reflecting “additional warning, contraindication, side-effect and precaution information” should be “placed into effect at the earliest possible time”. Such changes, according to Section 130.9(e), may be undertaken “by the applicant prior to his receipt of a written notice of approval of the supplemental new-drug applications...” Relying on this regulation, one court held: “Compliance with federal law did not prevent defendants from giving timely written warnings to the medical profession, either by means of Dear Doctor letters or through changes in their package inserts.” *McEwen v. Ortho Pharmaceutical Corporation*, *supra*, at 534. The successor version of this regulation is currently codified at 21 C.F.R. §314.70(c)(2)(i).
 - 10 The Fifth Circuit has rejected preemption as to FDA labeling determinations where withholding of material information from FDA has been alleged. *Hurley v. Lederle Laboratories*, 851 F.2d 1536, 1543 (5th Cir. 1988).
 - 11 *See, e.g.*, *Feldman v. Lederle Laboratories*, 234 N.J. Super. 559, 561 A.2d 288, 303–4 (1989), wherein the court ruled that if “information is withheld by the manufacturer, ... liability can exist notwithstanding FDA approval of the warning.” Referencing cases where defendants “failed to give the FDA information which they had in their possession and such failure contributed to the inadequacy of the warning,” the court noted that an “FDA approved warning is only as good as the information provided to it by the manufacturer.” *Id.* at 303. *See also* *Stanton v. Astra Pharmaceutical Prod. Inc.*, 718 F.2d 553, 571 n. 34 (3rd Cir. 1983), where one court concluded, in

the context of interpreting Comment k of Section 402(a) of the Restatement 2d of Torts, that a pharmaceutical company's failure to disclose certain drug related evidence to the FDA "rendered the product defective by depriving the FDA of information necessary to make an informed judgment concerning the conditions under which Xylocaine could be safely marketed." The court found that "[p]roper marketing would seem possible only when the FDA has received full information about the drug's characteristics and has made an informed decision to allow the manufacturer to market the drug." *Id.* Evidence of the manufacturer's failure to apprise the FDA in detail of adverse reaction information with regard to its drug was also held to be relevant to whether the FDA would have required further notice to physicians and whether such could bias that agency's proper evaluation of the drug. 718 F.2d at 567-570. In a similar vein, the court in *Toole v. Richardson Merrell, Inc.*, 60 Cal. Rptr. 398, 251 Cal. App.2d 689 (1967), held that, in light of a manufacturer's concealment from FDA of significant adverse findings from premarket animal studies "which, if known to the FDA, would have enabled its scientists to make a more critical analysis of MER/29, it can hardly be said that the FDA's permission to market the drug was an informed judgment, based on all the known facts, or that it was uninfluenced by appellant's non-disclosure." 60 Cal. Rptr at 412-413.

- 12 Examples of the failure of pharmaceutical manufacturers to advise FDA of adverse safety findings associated with use of their drugs have been cited in Sigelman, *Drug Safety Information from Foreign Countries*, *Trial*, March 1992, p. 20.

13 *See, e.g.*, §303(c)(1) of the Product Liability Reform Act, S. 1400, 101st Cong., 2d Sess., 1990.

- 14 Even an advocate for according preemptive force to FDA regulation preemption has recognized that the

final, and perhaps most critical, concern raised by preemption is the risk of administrative failure. That is, the FDA may make an inappropriate decision as to the marketing or labeling of a medication such that preemption will erroneously preclude the victims of such error from recovery.

Stoll, *A Question of Competence; the Judicial Role in the Regulation of Pharmaceuticals*, 45 *Food Drug Cosm. L.J.* 279, 297 (1990). In a similar vein, the Fifth Circuit held that FDA's decision as to the proper wording in labeling "must preempt by implication that of a state" where it has been assumed "that the FDA has processed all relevant and available information in arriving at the prescribed warning..." Hurley, *supra*, at 1542.

- 15 All of the Oraflex clinical trial patients who contracted liver disease had also developed kidney disease. Fourteenth Report, House Comm. On Government Operations, *Deficiencies in FDA's Regulation of the New Drug "Oraflex,"* H. Rep. No. 511, 98th Cong. 1st Sess. 9-12 (1983) [hereafter *Oraflex Report*].

16 *Id.* at 9.

- 17 In addition to four reports of combined kidney and liver disease, two other clinical trial reports of Oraflex-associated kidney disorders were submitted to Oraflex IND. *Id.* at 10.

18 *Id.*

19 *Id.* at 12.

- 20 *Id.* at 11. The Committee also found "FDA's lack of information on reports of Oraflex-associated deaths" to be "all the more surprising" because the FDA Commissioner had testified on August 3, 1982, that "the agency was conducting an intensive investigation of alleged adverse reaction reporting violations by Lilly in connection with Oraflex and several other investigational and marketed drugs." *Id.* at 11-12.

21 *See Drug Safety (Part 2)*, Hearings before a Subcomm. of the Comm. on Government Operations, 88th Cong., 2d Sess. (1964).

- 22 *Id.* at 582. By July 13, 1961, the manufacturer reported to FDA that it had received a total of 54 reports of hepatitis in patients, many of which involved death. *Id.* at 580.

23 Sigelman, *supra*.

- 24 For example, then FDA Commissioner Larrick testified that FDA later learned that McNeil had received a report of "fatal hepatitis in a patient on this drug even before we allowed the [new drug] application to become effective, but that report was not relayed to us until 1961." *Id.* at 568. In a similar vein, a September 1959 submission did not show that "instead of 32 cases of reversible liver

- damage, with 2 deaths probably unrelated to use of the drug, the firm then knew of 39 cases of hepatitis in patients taking Flexin, including 11 fatalities, and that 20 of the cases, including 6 deaths, had been ascribed directly to Flexin by the reporting physicians.” *Id.* at 577.
- 25 On June 11, 1958, a supplemental NDA for Flexin was submitted for the drug’s use as a uricosuric agent to treat gout. This statement was made in an accompanying brochure. *Id.* at 572.
- 26 *Id.* at 574.
- 27 *Id.* at 623.
- 28 *Id.* at 619.
- 29 According to then FDA Commissioner Larrick, the medical reviewer in charge of Flexin “had a great pile of mail on his desk, involving a great many other matters” and, as a consequence, neither he nor other medical reviewers “were aware of what was in the material that McNeil had reported at that time.” *Id.* at 623.
- 30 Specifically, the Oraflex and Flexin molecules contained a “benzoxazole” ring system as their nucleus. Oraflex Report, footnote 22 at 9.
- 31 *Id.*
- 32 Thirty-first Report, House Comm. on Government Operations, FDA’s Regulation of Zomax, H. Rep. No. 584, 98th Cong., 1st Sess. 15 (1983) [hereafter Zomax Report].
- 33 Seventy-First Report, House Comm. on Government Operations, FDA’s Deficient Regulation of the New Drug Versed. H. Rep. No. 1086, 100th Cong., 2d Sess. 21–22 (1988) [hereafter Versed Report].
- 34 *Id.* at 8.
- 35 FDA received the NDA for Orabilex on July 7, 1958 and approved it on October 24, 1958. FDA asked the manufacturer to withdraw Orabilex from the market in or about June 1964 in the wake of numerous reports of acute kidney damage associated with its use, including 25 deaths. During the hearings, FDA testified that it *began* a literature search to determine how many times Orabilex had been associated with kidney failure on May 10, 1962, only *after* the first such case had come to its attention on April 23, 1962. That search revealed nine reports of drug-associated renal toxicity in the literature. Drug Safety (Part 2), *supra*, at 685, 785–786, and 795.
- 36 Fifteenth Report, House Comm. on Government Operations, FDA’s Regulation of the New Drug Merital, H. Rep. No. 206, 100th Cong., 1st Sess. 37 (1987) [hereafter Merital Report].
- 37 Versed Report at 10–11.
- 38 *Id.* at 10–11 and 20.
- 39 *Id.* at 19–20.
- 40 *Id.* at 20–21.
- 41 *Id.* at 20.
- 42 FDA’s Regulation of the New Drug “Triazure”, Hearings before a Subcomm. of the Comm. on Government Operations, 94th Cong., 2d Sess. 1 (1976).
- 43 *Id.* at 4.
- 44 21 U.S.C. §355.
- 45 One post-market death from clotting had been reported, as had the amputation of a limb of another due to blood clots. *Id.* at 1. In addition, six other patients using Triazure developed blood clots. All but one of eight cases of serious thrombotic adverse reactions reported postmarketing were arterial and severe and some occurred in highly unusual sites such as the arm or middle toe. *Id.* at 70. These reactions had been reported among 500 to 1000 patients estimated to have used the drug. *Id.* at 63.
- There are faint echoes of the Triazure experience in FDA’s more recent approval of Tambocor (flecainide acetate), a drug intended to treat cardiac arrhythmias or irregular heart rhythms. By letter dated August 29, 1985, FDA advised the drug’s manufacturer that it believed that Tambocor should be approved only for *life-threatening* arrhythmias, because of its propensity to provoke new or more serious arrhythmias. FDA further advised the company that “[a]dditional study of flecainide in patients with these arrhythmias, including further and longer-term comparison with alternative agents, will be needed before use in such patients can be recommended.” Problems with FDA’s Regulation of the Antiarrhythmic Drugs Tambocor and Enkaid, Hearing before the Human Resources and Intergovernmental Relations Subcomm. of the Comm. on Government

Operations, 102d Cong, 1st Sess. 144–145 (1991). Nonetheless, on October 31, 1985, only two months later, FDA approved Tambocor for patients with less severe as well as life-threatening arrhythmias. *Id.* at 125 and 130. Subsequent to approval, the Cardiac Arrhythmia Suppression Trials (CAST) sponsored by the National Heart, Lung, and Blood Institute revealed a 2 1/2-fold increase in mortality among patients treated with Tambocor or Enkaid (encainide HCl) — another anti-arrhythmic agent — when compared with patients receiving a placebo. As a consequence, in April 1989, FDA requested labeling changes recommending against the use of Tambocor and Enkaid in less severe arrhythmias. *Id.* at 189.

46 *Id.* at 33.

47 *Id.*

48 *See* 21 C.F.R. §314.80.

49 Zomax Report at 11.

50 Zomax Report at 12.

51 Zomax Report at 13. Unanalyzed data contained in an FDA ADR [Adverse Drug Reaction] Highlight entitled “A Comparison of Anaphylactoid Reactions Associated with Nonsteroidal Anti-Inflammatory Drug,” revealed that, only seven months after Zomax was approved for marketing, the drug had already attracted 13.6% of the anaphylactoid reactions reported to FDA for its class even though by that time it had claimed, based on numbers of prescriptions filled, only 1.2% of market for that class.

52 Zomax Report at 16.

53 *Id.*

54 *Id.* at 16–17.

55 Thus, that labeling only contained a warning regarding patients who had allergically reacted in the past to aspirin or another drug in the same class as Zomax, which apparently constituted a distinct minority of the Zomax patients at risk for such a life-threatening side effect. Zomax Report at 19.

56 GAO/PEMD-90-15

57 These labeling changes typically involved limitation of the population for which these drugs are intended or addition of major warnings or precautions governing their use.

58 GAO recommended that

the Commissioner of FDA establish formal systemic procedures to assure that serious risks identified after a new drug has been approved are evaluated and *used to enhance premarketing review of clinical trials*. . . . We believe that the implementation of such procedures would, over the long run, *contribute to better and more timely labeling, in both the review process and postmarketing surveillance.* (Emphasis supplied)

Id. at 57.

59 *Toner v. Lederle Laboratories*, 112 Idaho 328, 732 P.2d 297, 311 n. 12 (1987).

60 *Id.*