Adequate Drug Warnings in the Face of Uncertain Causality: The Learned Intermediary Doctrine and the Need for Clarity

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ADEQUATE DRUG WARNINGS IN THE FACE OF UNCERTAIN CAUSALITY: THE LEARNED INTERMEDIARY DOCTRINE AND THE NEED FOR CLARITY

Michael Imbroscio
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I. INTRODUCTION

Given the extraordinary complexity of the human body, it is no surprise that we do not know all of the effects that stem from a given pharmaceutical product. Certain prescription drugs might turn out to be dangerous or even fatal to some users, while providing great benefits to others. Unfortunately, any time a drug with widespread application is accompanied by a known, albeit perhaps rare, side effect, chances are great that someone is eventually going to be


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harmed. Such risks can readily be disclosed in concrete terms so that physicians have the information necessary to balance the risks and benefits in deciding whether to prescribe the medication for any particular patient. In many situations, however, science has not yet definitively determined whether a purported side effect is causally connected with a particular medicine. The state of knowledge on such products is more limited — based, for example, on adverse incident reports and as yet inconclusive studies. This creates something of a conundrum when it comes to warnings on these products. On one hand, for warnings to fully apprise physicians of the dangers, they must have sufficient force. On the other, if the medical knowledge of a given drug, at a given time, is inconclusive, a warning that accompanies that product — assuming accuracy is desired — will obviously not be able to state a causal link. As such, while warnings can readily disclose known risks in concrete terms, warnings that apprise doctors of potential risks might by comparison appear more equivocal. Our focus is on the latter category.

In this short piece, we will argue that the absence of a proven causal connection should not preclude a warning from being adequate as a matter of law. We suggest that the impulse to categorically reject a warning as "equivocal" by virtue of an uncertain causal connection should be rejected. Instead, manufacturers in such circumstances should be able to accurately disclose what they know and, thereby, conform their conduct to a known rule of law. Furthermore, while the mere mention of an ailment standing alone will not necessarily absolve manufacturers of liability, when a warning reasonably describes the state of scientific knowledge regarding the specific condition that later befalls a patient, it should be given significant weight in the analysis.

In Part II, we will briefly survey the so-called learned intermediary doctrine. In Part III, we will analyze and critique the reasoning of a recent circuit opinion that declined to find a manufacturer’s warning adequate as a matter of law in light of an uncertain causal connection between the drug and the purported effects. In Part IV, we will further argue that such an approach should be rejected given that it ignores or minimizes: (i) whether or not the specific risk was described; (ii) the purposes of the learned intermediary doctrine; (iii) the

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1 One court gave the following cogent explanation:

[T]he reality is that when a medication causes a rare and serious side effect, the result is both frustrating and horrifying to the patient. Yet, from a public policy standpoint, our legal system has determined that so long as medical providers follow certain established precautions such as educating health-care providers, these calculated risks are acceptable given the tremendous benefits medicine can provide. As anyone who has had a family member’s life saved or improved through medication knows, modern medicine can be truly astonishing. It is unfortunate that on a rare occasion it carries with it catastrophic results.

position of the Food and Drug Administration; and (iv) the effects on manufacturers, doctors, and patients.

II. THE LEARNED INTERMEDIARY DOCTRINE

In general, manufacturers are strictly liable for the harm caused by products that are "unreasonably dangerous." However, as an exception to this principle, prescription drugs are considered "unavoidably unsafe" in that they are "quite incapable of being made safe for their intended and ordinary use." Recognizing this, the vast majority of states have adopted the "learned intermediary doctrine," under which a pharmaceutical manufacturer is not held liable if it provides an "adequate warning" to prescribing physicians, who, acting as "learned intermediaries," then apply their professional judgment to weigh the risks and benefits in individual cases. With respect to prescription drugs, "[t]he duty to provide adequate warnings arises only when the manufacturer knows or should know of a risk posed by the product" and "extends only to the medical profession, not the consumer."

The primary rationale for the learned intermediary doctrine is to assume a proper balance of responsibility between the doctor, who interacts with patients on an individual basis, and the manufacturer, which mass produces the drugs. As one court has noted,

2 Restatement (Second) of Torts, § 402A (1965).

3 Restatement (Second) of Torts, § 402A, cmt. k (1965) ("There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs."); see, e.g., Ziliak v. AstraZeneca LP, 324 F.3d 518, 521 (7th Cir. 2003) (applying Indiana law).


5 Ziliak, 324 F.3d at 521.

6 See, e.g., Garside v. Osco Drug, Inc., 976 F.2d 77 (1st Cir. 1992) ("[T]he rationale underlying the prescription drug rule is that the prescribing physician, as the 'learned intermediary' standing between the manufacturer and consumer/patient, is generally in the best position to evaluate the potential risks and benefits of ingesting a certain drug and to advise the patient accordingly. Under this doctrine, the manufacturer's duty is fulfilled once it adequately warns the physician.")
Prescription drugs are likely to be complex medicines, esoteric in formula and varied in effect. As a medical expert, the prescribing physician can take into account the propensities of the drug as well as the susceptibilities of his patient. His is the task of weighing the benefits of any medication against its potential dangers. The choice he makes is an informed one, an individualized medical judgment bottomed on a knowledge of both patient and palliative.7

The learned intermediary defense consists of two hurdles that the plaintiff must overcome for a court to hold the manufacturer liable. To avoid summary judgment, the plaintiff must put forth evidence (a) that the warning is inadequate and (b) that the deficiency is the proximate cause of the plaintiff's injuries.8

While the focus of this Article is on the first prong, sometimes the two become muddled, so for clarity we will first briefly describe the second. Under the second prong, even if the warning is inadequate, the causal chain is broken if the outcome would remain unchanged with an adequate warning.9 In other

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7 Reyes v. Wyeth Labs., 498 F.2d 1264, 1276 (5th Cir. 1974); see also Ferrara v. Berlex Labs., Inc., 732 F.Supp. 552, 555 (E.D. Pa. 1990) ("The rationale behind this doctrine is simply stated. In the dispensing of prescription drugs, the physician is required to act as a learned intermediary between the manufacturer and patient because of the complexity of medicines and the doctor's medical knowledge."). aff'd 914 F.2d 242 (3d Cir. 1990).

8 See, e.g., Motus v. Pfizer, Inc., 196 F. Supp. 2d 984, 991 (C.D. Cal. 2001) ("A plaintiff asserting causes of action based on a failure to warn must prove not only that no warning was provided or the warning was inadequate, but also that the inadequacy or absence of the warning caused the plaintiff's injury." (citations omitted)), aff'd 358 F.3d 659 (9th Cir. 2004); In re Rezulin Prods. Liab. Litig., 331 F. Supp. 2d 196, 199 (S.D.N.Y. 2004) ("A plaintiff in a prescription drug failure to warn case therefore has the burden of proving that (1) the warning to the physician was defective, and (2) the inadequate warning proximately caused the plaintiff's injury, i.e., that adequate warnings would have persuaded the physician not to prescribe the drug in question." (applying Texas and Mississippi law)).

Some states adopt a rebuttable presumption such that "once the plaintiff establishes that the manufacturer provided inadequate warnings, the burden shifts to the defendant to show that an adequate warning would not have affected the doctor's conduct in prescribing the drug" while "in states that have not adopted the rebuttable presumption, the plaintiff in a prescription drug case bears the full burden of proving through affirmative evidence that the inadequate warning was the proximate cause of the injury." Motus, 196 F. Supp. 2d at 991; see, e.g., Thom, 353 F.3d at 855 (employing rebuttable presumption in application of Wyoming law); Ralston v. Smith & Nephew Richards, Inc., 275 F.3d 965, 977 n.6 (10th Cir. 2001) (same, Kansas law).

9 See, e.g., Motus v. Pfizer Inc., 358 F.3d 659, 660–61 (9th Cir. 2004) ("[E]ven if Pfizer's warnings concerning Zoloft and suicide were deficient, on the facts of this case, Motus failed to establish that Pfizer's allegedly inadequate warnings contributed to her husband's suicide."); Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806 (5th Cir. 1992)
words, if the doctor would have prescribed the drug regardless, proximate causation is lacking.\textsuperscript{10} For example, the doctor might have been fully apprised of the risks from an independent source and, in her best judgment, concluded that the benefits outweighed the risks.\textsuperscript{11} Alternatively, whether or not fully informed, the doctor's decision might have been impervious to the strength of the warning.\textsuperscript{12} In some cases, the doctor fails to read the warnings at all.\textsuperscript{13}

Turning now to the first prong, an adequate warning is one that is reasonable under the circumstances.\textsuperscript{14} While often a factual question for the jury, courts routinely find warnings adequate as a matter of law.\textsuperscript{15} In Ziliak v. Astra-
Zeneca, for example, the Seventh Circuit had little difficulty in finding a warning adequate where the doctor was reasonably made aware of the specific risk that ultimately materialized.\textsuperscript{16} One common formulation of the doctrine states that a warning is adequate as a matter of law if it is "accurate, clear and unambiguous."\textsuperscript{17} On the flip side, summary judgment on this issue is not proper if, as one court put it, the warning did "not convey a fair indication of the nature of the dangers involved, was reluctant and equivocal in tone and lacked a sense of urgency."\textsuperscript{18}

However, it may be far from "clear and unambiguous" how to meet this standard when the causal connection between the drug and a type of affliction is uncertain. One recent case, Thom\textsuperscript{19} v. Bristol-Myers Squibb,\textsuperscript{19} suggests that when the manufacturer's warning fails to unequivocally state that a drug can cause the plaintiff's affliction the warning cannot be adequate as a matter of law — even when there is no evidence either that the manufacturer knew of a causal connection or, indeed, that a causal connection exists at all.\textsuperscript{20}

The thrust of this article is that, while it is true that a causal link between a drug and a purported side effect might be unknown to the manufacturer or to science in general, it should nonetheless be possible for a pharmaceutical company's warning to be adequate as a matter of law — by reasonably conveying the current state of knowledge regarding potential risks. When a company is


\textsuperscript{16} \textit{Ziliak}, 324 F.3d at 521 (noting that "pharmaceutical manufacturer [had] warned doctors that specific adverse side effects are associated with the use of a drug"); \textit{see also} RaIston v. Smith & Nephew Richards, Inc., 275 F.3d 965, 976 (10th Cir. 2001) ("[T]he warnings provided by Smith & Nephew reasonably cautioned against each of the specific risks alleged by RaIston.").

\textsuperscript{17} \textit{Felix}, 540 So.2d at 105; \textit{see also} Pittman, 890 S.W.2d at 429 ("The adequacy of a drug manufacturer's warning . . . becomes a question of law only when the instructions are accurate and unambiguous."). In \textit{Pittman}, the court cites five criteria in holding that a warning was adequate:

1. the warning must adequately indicate the scope of the danger; 2. the warning must reasonably communicate the extent or seriousness of the harm that could result from misuse of the drug; 3. the physical aspects of the warning must be adequate to alert a reasonably prudent person to the danger; 4. a simple directive warning may be inadequate when it fails to indicate the consequences that might result from failure to follow it and, . . . 5. the means to convey the warning must be adequate.

\textit{Id.} (quoting Serna v. Roche Labs., 684 P.2d 1187, 1189 (N.M. App. 1984)).


\textsuperscript{19} 353 F.3d 848 (10th Cir. 2003).

\textsuperscript{20} \textit{Id.} at 857–58 (10th Cir. 2003) (applying Wyoming law).
able to conform to a known rule of law, all parties are better off and the principles driving the learned intermediary doctrine are vindicated.

III. THOM v. BRISTOL-MYERS SQUIBB CO.

Steven Thom sought treatment for depression and sleep difficulties. Unfortunately, after taking a prescription anti-depressant called Serzone, manufactured by Bristol-Myers Squibb ("BMS"), he developed a condition known as "priapism" — a "persistent erection of the penis, accompanied by pain and tenderness, resulting from a pathologic condition rather than sexual desire." Mr. Thom, now left with permanent penile injury, brought suit against BMS.

In this case, BMS had included an FDA-approved package insert specifically warning doctors that "rare reports of priapism have been received since market introduction." The trial court granted summary judgment to the manufacturer noting that "[q]uite simply, a manufacturer should not be held liable for having failed to warn in an instance where, in fact, it warned of the very injury of which plaintiff complains." It rejected the plaintiffs' contention that the warning should have been stronger because "[w]hen a warning as to a particular

21 Id. at 850.
22 Id. (quoting STEDMAN'S MEDICAL DICTIONARY 1425 (26th ed. 1995)).
23 Id. As described by the court, the physician package insert, at the time Serzone was prescribed to Mr. Thom, read in pertinent part:

PRECAUTIONS

Priapism
While priapism did not occur during pre-marketing experience with nefazodone [the scientific name of Serzone], rare reports of priapism have been received since market introduction. A causal relationship to nefazodone has not been established (see ADVERSE REACTIONS Section). If patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physicians. If the condition persists for more than 24 hours, a urologist should be consulted to determine appropriate management.

ADVERSE REACTIONS

Postintroduction Clinical Experience
Post marketing experience with SERZONE has shown an adverse experience profile similar to that seen during the premarketing evaluation of nefazodone. Voluntary reports of adverse events temporally associated with SERZONE have been received since market introduction that are not listed above and for which a causal relationship has not been established. These include:

Rare occurrences of . . . priapism (see PRECAUTIONS Section).

risk has been provided, a demand for a stronger or more prominent warning is not supported by the law.\textsuperscript{25}

The Tenth Circuit reversed, finding that the adequacy of the warning was a question of fact for a jury.\textsuperscript{26} The court supplied three reasons in support of this conclusion. First, the language on the package insert was too “equivocal” to be adequate as a matter of law.\textsuperscript{27} Second, there is a “factual controversy regarding the state of BMS’s knowledge of priapism” and the relationship between Serzone and another BMS drug.\textsuperscript{28} Third, “there is also a dispute as to whether the instruction to seek medical treatment accurately conveyed the magnitude of the harm, and whether it caused confusion when following the instruction to discontinue treatment.”\textsuperscript{29} Each of these reasons fails to withstand scrutiny and we consider each in turn.

First, the court found the warning to be too “equivocal” to qualify for adequacy as a matter of law.\textsuperscript{30} Providing little analysis, the court did not directly explain why it was too equivocal.\textsuperscript{31} It first noted that “[t]he mere mention of a possible injury . . . is not necessarily adequate.”\textsuperscript{32} It then seemed to imply that the failure to be adequate as a matter of law was rooted in the warning’s failure to state a causal relationship between priapism and nefazodone (the scientific name of Serzone).\textsuperscript{33} After pointing out that the Serzone warning failed to state a causal connection,\textsuperscript{34} the court cited cases where the respective warnings “did not unequivocally state that there was a causal relationship,” stated that a “causal relationship has not been established,” and stated that adverse effects were “unconfirmed.”\textsuperscript{35} Thom contrasted these with warnings that “stated [that a] potentially ‘life-threatening’ side effect was reported and indicated the pri-

\textsuperscript{25} Id. at 11 (citing Caveny v. CIBA-GEIGY Corp., 818 F.Supp. 1404, 1406 (D. Colo. 1992)).

\textsuperscript{26} Thom, 353 F.3d at 853–55.

\textsuperscript{27} Id. at 853–54.

\textsuperscript{28} Id. at 854.

\textsuperscript{29} Id. at 855.

\textsuperscript{30} Id. at 853–54.

\textsuperscript{31} Id.

\textsuperscript{32} Id. at 853 (citing Stahl v. Novartis Pharms. Corp., 283 F.3d 244, 266–67 (5th Cir. 2002) (interpreting the Louisiana Products Liability Act)).

\textsuperscript{33} Id. at 853–54.

\textsuperscript{34} Id. at 853 (“[T]he package insert for Serzone indicated only that ‘rare reports’ of priapism were ‘temporally associated’ with Serzone; it further stated that a ‘causal relationship [of priapism] to nefazodone has not been established.’”).

mary cause and management of it” or “noted that a ‘causal relationship [was] probable.’” 36 In other words, it appears that the court was unwilling to consider any warning adequate if it expresses a lack of causation because such a warning would be too equivocal. This approach effectively rules out adequate warnings as a matter of law for any product where there have been anecdotal reports of potential side-effects, but where a causal connection does not exist — or at least has not yet been proven — even if the warnings effectively convey the extent of the manufacturer’s knowledge. 37

Second, the court found a factual controversy as to BMS’s knowledge of Serzone, which in turn bears on the adequacy of its warning. 38 However, the court pointed to no evidence offered by the plaintiffs that would show a causal connection between Serzone and priapism — let alone BMS’s knowledge of such a connection.

At most, the evidence demonstrates that BMS knew of a similarity between Serzone and an earlier drug called trazodone, and that there is an “association” between trazodone and priapism. 39 Even assuming that Serzone and trazodone are identical, this merely shows that BMS constructively knew of an association between Serzone and priapism. Of course, an “association,” demonstrated, for example, via adverse incident reports, stops far short of establishing causation. 40


37 Regulations require manufacturers to submit certain “adverse drug experience” reports, also known as “adverse incident reports,” to the FDA. See 21 C.F.R. § 310.305 (2002); 21 C.F.R. § 314.80 (2004). An “adverse drug experience” is “[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related.” 21 C.F.R. §§ 310.305(b), 314.80(a). Such reports do not constitute “an admission that the drug caused or contributed to an adverse effect.” 21 C.F.R. §§ 310.305(g), 314.80(k). The FDA also receives voluntary reports of adverse events from health care professionals and consumers. See, e.g., 69 Fed. Reg. 21,778, at 21,789 (Apr. 22, 2004) (“While drug manufacturers are required to notify FDA of certain adverse drug events, reports from individuals and health care professionals are voluntary.”).

38 Thom, 353 F.3d at 854 (“Because the duty to warn arises only when the manufacturer knows or should know of the risk, the adequacy of a warning is commensurate with the manufacturer’s knowledge of the effects of the drug.”). In acknowledging this fact, the court should have noticed the tension between requiring a warning commensurate with the defendant’s knowledge and requiring a statement of causation regardless of the defendant’s knowledge (i.e., finding any warnings lacking such a statement to be too “equivocal”).

39 Id. (“A little over a year after trazodone was introduced into the marketplace, published peer review medical articles began reporting the association between trazodone and priapism.” (emphasis added) (citing Gerald M. Aronoff, Trazodone Associate with Priapism, 1 LANCET 856 (1984); Maryonda Scher et al., Trazodone and Priapism, 140 AM. J. OF PSYCHIATRY 1362 (1983)).

40 David H. Kaye & David A. Freedman, Reference Guide on Statistics, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 91 (Federal Judicial Center, 2d ed. 2000) (“Observational studies can establish that one factor is associated with another, but considerable analysis may be necessary to bridge the gap from association to causation.”); see also id. (“Anecdotal evidence’ means reports of one kind of event following another. Typically, the reports are obtained haphaz-
In any case, such an association had already been admitted by BMS on the package insert: priapism had been "temporally associated with SERZONE" in "[v]oluntary reports of adverse events." The introduction of trazodone into the equation did little more than inject an irrelevant question of fact into the mix. Even assuming a complete identity between the two drugs and BMS's knowledge thereof, it should not detract from the warning's adequacy because none of the evidence cited indicates that BMS knew of a causal link (or indeed that such a link exists) — merely an "association" — between the drug and the adverse incident. Therefore, the court's argument that "such evidence is relevant in determining the adequacy of the Serzone warning because it goes to the state of BMS's actual and constructive knowledge of the risk of priapism from a drug BMS admits to 'hav[ing] some structural similarity' with Serzone" is unpersuasive.

Third, the court found a question of fact as to "whether the instruction to seek medical treatment accurately conveyed the magnitude of the harm, and whether it caused confusion when following the instruction to discontinue treatment." However, the warning appears rather clear: "[i]f patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physician." Even without this urgent directive, a certain amount of common sense suggests what constitutes a "prolonged or inappropriate" length of time in these circumstances. The court placed great weight upon the subsequent sentence which states that "[i]f the condition persists for more than 24 hours, a urologist should be consulted to determine appropriate management," and asserts that this creates a question of fact because there is evidence suggesting that the "state of the medical knowledge is that priapism linked with prescription drug use can result in permanent penile injury and impotence if not treated within four to eight hours after its onset." The court pointed to the affidavit of Thom's urological expert and two medical articles to support this proposition. However, the court did not indicate that the evidence attested to the state of medical knowledge at the time of Thom's prescription. Indeed, as the court noted, the medical articles it cited "were pub-

ardly or selectively, and the logic of 'post hoc, ergo propter hoc' does not suffice to demonstrate that the first event causes the second. Consequently, while anecdotal evidence can be suggestive, it can also be quite misleading.

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41 Id. at 850.
42 Id. at 854–55 n.1. The court even notes that the "evidence of trazodone's association with priapism is not being used to show that Serzone actually caused priapism."
43 Id. at 855.
44 Id. (emphasis added).
45 Id.
46 Id.
lished well after Mr. Thom was prescribed Serzone.” 47 Because, as one court noted, “[a] manufacturer can only be required to warn of risks known during the time in which the plaintiff was using the product in question,” the finding of a material fact on this point is questionable. 48

In any case, whether the maximum length of time to avoid permanent damage is four hours or twenty-four, either one should suffice to put physicians on notice of a significant, specific, and urgent risk that might arise. It is generally not up to the manufacturer to prescribe treatment for potential side effects. 49 Instead, the physician uses her best judgment in deciding whether to prescribe the drug in light of the particular patient’s unique circumstances. The physician also has the primary responsibility to set up a plan for discontinuing treatment in the event of an adverse reaction — including determining how long is too long. Assuming that BMS did not misrepresent its knowledge — and there is little or no evidence that it did — there is still no material question of fact with regard to the adequacy of the warning. 50

Given that Thom’s second and third supporting rationales are questionable, the primary rationale seems to be the first — the “equivocal” nature of the warning. The implication of Thom, then, is that absent an unequivocal statement of causation between a drug and purported side effects, a warning cannot be adequate as a matter of law. In the next part, we suggest that this approach should be rejected.

IV. ADEQUACY IN THE FACE OF CAUSAL UNCERTAINTY

Courts should hesitate to follow Thom when confronted with warnings that profess to something less than a causal connection. The Thom approach gives insufficient consideration to the warning’s specific description of the risk. It is also in tension with the purposes of the learned intermediary doctrine. Finally, it places manufacturers in a difficult position with respect to the FDA and poses risks to doctors and patients.

47 Id. at 855 n.2. The court also pointed to an affidavit wherein Thom’s urological expert indicated that “low-flow priapism is a medical emergency that requires medical intervention and resolution within four to eight hours of the onset in order to prevent permanent injury.” However, there is no mention of how recently the expert (or science in general) came to this conclusion.


49 See, e.g., Ziliak v. Astra Zeneca, 324 F.3d 518, 521 (7th Cir. 2003).

50 See also Martin v. Hacker, 83 N.Y.2d 1, 11–12 (1993) (citations omitted) for the proposition that even if the time period mentioned in the warning is seen as creating some confusion, “contradictions will not create a question of fact as to the warning’s adequacy, if the language of a particular admonition against a side effect is precise, direct, and unequivocal and has sufficient force.”
A. Specific Risk Described

We first want to examine the role that a description of a specific adverse effect will play in the adequacy of a warning. On one hand, we are not suggesting that the mere mention of a possible injury is necessarily adequate. However, even when a causal connection is unknown (and perhaps especially in such cases), courts should place significant weight on whether the warning describes what the manufacturer knows about the specific adverse effect that a plaintiff later alleges. In conveying specific reports of maladies associated with the drug (even if there is not enough to prove causation), such a warning will serve its purpose of informing the physician so that she can make a reasoned judgment in deciding whether or not, in light of the possible connection between the drug and the adverse reports, to prescribe the drug. In Thom, the Serzone warnings twice described the possibility of priapism — the exact adverse effect suffered by Mr. Thom — in addition to expressing urgency and providing instructions in the event of a prolonged erection. Nonetheless, the Thom court did not find it adequate as a matter of law.

In contrast, numerous courts have found it highly significant — if not dispositive — that the defendant warns of the specific risk in question. In Ziliak, for example, where the plaintiff had developed glaucoma, cataracts, and high intraocular pressure, the court found an adequate warning which stated that “rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.” Other courts, while recognizing the significance of the specific mention of a risk, found a warning inadequate for other reasons.

53 See, e.g., Austin v. Will-Burt Co., 361 F.3d 862, 868 (5th Cir. 2004) (“In Mississippi, a warning may be held adequate as a matter of law where the adverse effect was one that the manufacturer specifically warned against.” (citing Cather v. Catheter Tech. Corp., 753 F.Supp. 634, 640 (S.D. Miss. 1991))); Ziliak, 324 F.3d at 521 (holding warning adequate where manufacturer “warn[ed] doctors that specific adverse side effects are associated with the use of a drug”); Vitanza v. Upjohn Co., 48 F. Supp. 2d 124, 132 n. 9 (D. Conn. 1999) (“The plaintiff does not appear to contest the adequacy of the defendant's [warnings] to the medical community or to [the physician] directly, nor could she, given that the defendant warned of the specific risk at issue in this case.”); but see Erony v. Alza Corp., 913 F. Supp. 195, 200 (S.D.N.Y. 1995) (question of fact where the warning instructed to keep out of reach of children and warned that severe hypoventilation could result and require medical treatment, but did not say that the resulting complications could be serious enough to result in death).
54 Ziliak, 324 F.3d at 519.
55 See, e.g., Golod v. Hoffman La Roche, 964 F.Supp. 841, 853–54 (S.D.N.Y. 1997) (question of fact where plaintiff lost eyesight and “the package inserts did specify the general type of side effect—corneal abnormalities and iritis—that led to the demise of Golod's eye . . . [but] indicated that the side effects were temporary and resolved after [drug use] was discontinued”).
As in Ziliak, it might well be appropriate for a warning to describe specific effects as "rare." As long as it conveys the manufacturer's constructive knowledge, such a warning gives the prescribing physician an accurate picture of the risks associated with the drug so that she can make an informed decision. In Plummer v. Lederle Laboratories, for example, the warnings stated that

[p]aralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasions, reported in individuals receiving the vaccine, as well as in persons who were in close contact with vaccines. . . . The risk of a vaccine-associated paralysis is extremely small for vaccines, susceptible family members and other close personal contacts.56

In Plummer, the causal connection between the vaccine and the adverse effect was known, and the rate of incidence was known to be infrequent.

However, there is scant difference between knowing a risk to be definite albeit minute and saying so (as in Plummer) and knowing that only few cases of an adverse effect were reported — but not knowing if they are causally related — and similarly saying so (as with priapism in Thom). In each case, the warning provides doctors with the most accurate information available so that the doctor can use her expert judgment in deciding whether or not to prescribe the drug. As such, Thom's insistence on something more makes very little sense. Courts should be willing to find a warning adequate as a matter of law as long as a manufacturer accurately conveys its knowledge of the drug — even if the potential harm has only been observed infrequently and even if the manufacturer is unable to definitively state a causal connection — especially if the manufacturer warned of the specific condition for which the plaintiff later brought suit.

This is not to say that a warning must necessarily mention the specific condition that a plaintiff later complains of in order to be an adequate warning as a matter of law. In some cases, it might be impractical or impossible to name all possible specific risks — either because they are too numerous or because they are unknown.57 Along these lines, one court found a warning adequate because "[t]he physician was told under no circumstances to inject the drug into subcutaneous tissue, although he was not told that necrosis might result from his violation of this instruction," rejecting the notion that "‘the duty of the defen-

56 Plummer, 819 F.2d 349, 352 (2d. Cir. 1987) (emphasis added) ("Even assuming . . . that the warnings did minimize the risk of contracting contact polio, the fact remains that the probability of contracting either contact polio or wild polio is extremely remote.").

57 See, e.g., Ralston v. Smith & Nephew Richards, Inc., 275 F.3d 965, 976 (10th Cir. 2001) ("While Ralston prefers that these warnings be more specific, Kansas law does not require that a warning warn against every conceivable risk under every conceivable circumstance. Rather, as already discussed, Kansas requires only that the warnings be ‘reasonable under the circumstances.’ Here, the warnings . . . reasonably cautioned against each of the specific risks alleged." (citations omitted)).
dant extended to explaining exactly how the danger against which he had been warned might operate."

In sum, when a court is faced with evaluating the adequacy of a warning with regard to a condition with an uncertain causal link to the drug, the manufacturer might be unable to make many concrete statements, having to rely on inconclusive studies and informal observations. In such a context, therefore, it makes sense to place significant weight on the fact that a warning specifically describes a condition that later becomes subject of a lawsuit, even if that description does not state a causal connection.

B. Purpose of a Learned Intermediary

As previously explained, the learned intermediary doctrine represents a distribution of responsibility between the drug manufacturers and the doctors, where each side understands the other's role. Even when the causal effects of a given drug are uncertain, the manufacturer's duty is to provide the doctor with what it knows about the drug; it is the doctor's place to utilize this information. Thom undermined this balance by effectively precluding a warning from being adequate when the underlying science is uncertain. Under Thom's approach, a drug company cannot be sure that it has discharged its duty, creating a tendency to "overwarn." In turn, a doctor will not be sure that the warnings represent accurate information and might either under-prescribe certain drugs or inappropriately discount all warnings.

In Thom, the court also upset the balance between manufacturers and doctors when it transferred a portion of the responsibility for developing an appropriate monitoring regimen. The manufacturer's blanket statement of seeking help "immediately" should not be read as a substitute to a physician's expert knowledge, but as a signal to a learned intermediary. In contrast to Thom, the court in Ziliak more readily assumes that the doctor is competent to perform his role: "If a pharmaceutical manufacturer warns doctors that specific adverse side effects are associated with the use of a drug, then . . . implicit in the warning . . . is the doctor's need to monitor the patient and to consider alternative therapies." The court also emphasizes that the doctor "took the risks that Ziliak would develop adverse side effects into account when prescribing [the drug]."


59 See, e.g., Brooks v. Howmedica, Inc., 273 F.3d 785, 797 (8th Cir. 2001) ("Trials of tort claims pose incentives to overwarn: the visible monetary costs of additional warnings are typically quite low—a few pennies for a bit more paper and a little more ink."); (quoting James A. Henderson & Aaron D. Twerski, Doctrinal Collapse in Products Liability: The Empty Shell of Failure to Warn, 65 N.Y.U. L. REV. 265, 297 (1990))).

60 Ziliak v. Astra Zeneca, 324 F.3d 518, 521 (7th Cir. 2003).

61 Id. It is curious that the court in Thom did not even mention Ziliak, even though the latter is a sister circuit's recent pronouncement on the learned intermediary doctrine, handed down only a
Even when there is no scientific proof of causation, the purposes of the learned intermediary doctrine are best served if courts recognize that a warning can still be adequate as a matter of law if the manufacturer discharges its duty by informing the doctor of what it knows.

C. The FDA

Allowing adequacy in the face of causal uncertainty also comports with the FDA’s oversight of prescription drugs. In contrast, the Thom approach, by implicitly requiring a statement of a causal connection even when causation is unknown as a prerequisite to finding a warning adequate as a matter of law, places defendants in an untenable position with respect to FDA regulations.

Warning labels must be FDA-approved as part of a new drug application and any changes to a prescription drug’s labeling must be approved by the FDA.62 Failure to secure approval can result in a determination that the drug is “misbranded” and can be accompanied by regulatory and enforcement actions, including injunction,63 seizure,64 and criminal prosecution.65 One court summarized the regulations as follows:

The FDCA prohibits a drug manufacturer from marketing a new drug unless the FDA has approved the drug as both safe and effective for its intended use. In addition to scientific and experimental data, a new drug application must include a proposed label. If the FDA determines that the labeling is false or misleading in any way, the drug is deemed “misbranded,” and the FDA will reject the application for approval of the drug. Once an application has been approved, any change in the labeling requires a supplement to the application and approval by the FDA, either before or after the change.66

FDA regulations do allow for limited circumstances in which manufacturers may make temporary labeling changes prior to FDA approval, but they are sub-

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ject to subsequent approval or rejection by the FDA. However, the approval required for a labeling change — even to comply with state requirements that purport to impose liability — is not always readily forthcoming. Daniel Troy, who was then Chief Counsel of the FDA, once opined: “You can’t put anything on the label without coming to us first or getting our blessing . . . . We have absolute control over the label.” He furthermore argued that, absent proof of scientific causation — and particularly when the FDA has itself specifically failed to find causation — it is inappropriate to include statements of causation in the warning materials: “[E]nhancing the warnings in the labeling of SSRIs [selective serotonin reuptake inhibitors] in the absence of scientific evidence actually could be misleading and could misbrand the drugs under . . . the FDCA.” These comments, made in the larger context of the ongoing debate over the preemptive effect of FDA labeling requirements, serve to highlight the potential difficulties that a pharmaceutical company could face in the event that it attempted to alter the label on products with uncertain causal effects.

At the same time, the FDA has made it clear that it can require a warning even absent proof of causation if it sees fit. In one such instance, the FDA

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67 See 21 C.F.R. § 314.70(c)(6). This section provides:

The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement [i.e. a request] for the change. These changes include, but are not limited to:

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction.[]

Id. This version of the provision appeared at 21 C.F.R. § 314.70(c)(1) (2003).

68 See Dowhal, 32 Cal. 4th at 921; Daniel E. Troy, FDA Involvement in Product Liability Lawsuits, FDLI UPDATE 4 (Jan./Feb. 2003) (“FDA has prohibited manufacturers from labeling their products voluntarily with a [state law] warning. . . . [U]sing additional warning language . . . could render their products misbranded under the . . . FDCA.”).


70 Troy, supra note 68, at 6 (citing 21 U.S.C. § 352(a)).

71 The topic of federal preemption is beyond the scope of, albeit related to, this piece. For a discussion of preemption, see, e.g., David G. Owen, Federal Preemption of Products Liability Claims, 55 S.C. L. REV. 411 (2003).

72 Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, 67 Fed. Reg. 72,555, 72,556 (Dec. 6, 2002) (“To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.”).
explained this decision based in part on the magnitude of the risk: "The agency recognizes that the number of reports is small compared to the total doses used. However, there is a particular concern because of the reports of toxic psychosis, especially in children . . . ."73 The report goes on to note that "[t]his judgment balances the benefits of these drug products against their potential risks, and reflects our conclusion that even a potential link between the overuse of diphenhydramine and serious adverse health consequences warrants this action."74 Such judgments are appropriately within the purview of the FDA, which, as the public health agency with expertise in the field, is better situated than generalist courts to assess prescription drug causality and labeling requirements.75 The Supreme Court has often had occasion to comment on the superior position of agencies in general and the FDA in particular, in matters requiring specialized expertise.76 The Thom approach, however, encourages court-defined rather than

73 67 Fed. Reg. at 72,555.
74 67 Fed. Reg. at 72,556 (citing 21 C.F.R. § 330.10(a) (2002)).
75 The FDA explained its view, as quoted in a recent preemption case involving medical devices, as follows:

[It is inappropriate for a jury to second-guess FDA's scientific judgment on such a matter that is within FDA's particular expertise. . . . The agency makes a reasoned and deliberate decision as to the correct pathway of regulation and whether to approve the device. Juries lack the scientific knowledge and technical expertise necessary to make such judgments. . . .

[T]he prospect of hundreds of individual juries determining the propriety of particular device approvals, or the appropriate standards to apply to those approvals, is the antithesis of the orderly scheme Congress put in place and charged the FDA with implementing.

Such uncertainty as to the status of medical devices would create chaos for both the regulated industry and FDA.

Horn v. Thoratec Corp., 376 F.3d 163, 178 (3d Cir. 2004) (first ellipse added) (other alterations in original) (citation omitted).
76 See, e.g., Baltimore Gas & Elec. Co. v. Nat'l Resources Defense Council, Inc., 462 U.S. 87, 103 (1983) ("When examining this kind of scientific determination [by a federal agency] . . . a reviewing court must generally be at its most deferential."); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653–54 (1973) ("Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background. The determination whether a drug is generally recognized as safe and effective [under the Food, Drug, and Cosmetic Act] necessarily implicates complex chemical and pharmacological considerations. Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand."); Far East Conference v. United States, 342 U.S. 570, 574–75 (1952) ("In cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. . . . Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience,
FDA-defined warnings. This places drug companies in a difficult position, sandwiched between the risk of liability on one hand and the risk of an FDA violation for “misbranding” on the other.

D. Effects on Manufacturers, Doctors, and Patients

If courts insist on an unequivocal statement of causation, discounting the possibility that warnings on drugs with uncertain effects will be adequate as a matter of law, it could impair the interests of manufacturers, doctors, and consumers. First, a manufacturer of such drugs will be unable to know in advance what it is required to include in its warning. The manufacturer will face an increased risk of liability because — no matter what language is used in a warning — a jury might find it inadequate. Second, insofar as this results in warnings with unwarranted statements of causation, doctors’ ability to rely on the warnings for an accurate picture of the risks involved will be impaired. A warning attesting to a causal relationship conveys a very different message to the doctor than one that says there have been reports of a temporal association. If concrete statements of causation are required across the board, it will be difficult to distinguish between the known effects and the suspected effects, thus impairing doctors’ ability to use their reasoned judgment to make decisions in individual cases. Doctors will be relying on warnings dictated by the courts rather than by science. Third, such warnings could lead to under-prescription of drugs, depriving patients of their benefits.  

Instead, the Thom approach should be rejected in favor of an approach that allows manufacturers to conform their conduct to a known rule of law — placing significant emphasis on whether the potential for a specific adverse effect is accurately, clearly and unambiguously described in the warning. This would encourage manufacturers to provide accurate warnings even when causation is uncertain (as in Thom) and would encourage doctors to use their reasoned judgment in such cases to balance the risks and benefits.

V. Conclusion

Scientific causation is often uncertain when it comes to the side effects of drugs. Even when causation is fuzzy, however, courts should recognize that there must be some set of warnings that the manufacturer can include such that they are adequate as a matter of law to inform a learned intermediary of the risks known at that point in time — especially when the warnings describe a specific risk that later materializes. Courts should apply the learned intermediary doctrine in a way that encourages manufacturers to disclose what they know —

77 See Troy, supra note 68, at 6 (arguing that “overwarning presents a substantial risk of discouraging” the use of drugs in appropriate cases).
whether or not that disclosure reveals a causal connection. If courts insist on a statement of causation even when such a link is uncertain, it will subvert the purposes of the learned intermediary doctrine, place manufacturers in an untenable position facing the FDA on one side and a jury on the other, and impair the interests of doctors and patients.