**Case No. 1210140**

**IN THE SUPREME COURT OF ALABAMA**

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**MARK BLACKBURN, et al.,**

**Plaintiff-Appellant**

**v.**

**SHIRE U.S., INC.; SHIRE, LLC,**

**Defendants-Appellees**

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**On Certified Questions from the United States Court of Appeals for the Eleventh Circuit,**
**20-12258**

**District Court:**
**No. 2:16-CV-00936-MHH**

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# PLAINTIFF-APPELLANT BLACKBURN'S REPLY TO DEFENDANT SHIRE'S RESPONSE TO CERTIFIED QUESTIONS

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COMES NOW Plaintiff-Appellant Mark Blackburn ("Blackburn") and replies to Defendants-Appellees Shire US Inc. and Shire LLC's ("Shire") Response Brief on Certified Questions.

## I. INTRODUCTION AND SUMMARY OF ARGUMENT

The two discrete questions of Alabama law certified to this Court by the Eleventh Circuit address whether a drug manufacturer must provide adequate instructions for safe use as part of its duty to warn and whether proximate cause may be established when the treating physician, who unknowingly prescribed the drug with unsafe instructions, still would have prescribed the drug with safe instructions. In its Response, Shire asks the Court to contravene existing law to answer both questions in the negative but cites no applicable authority to support doing so.

Question One: Shire's Response to Question One ignores the established twofold nature of a drug manufacturer's duty to warn under

Alabama law. The drug maker has the duty to warn of side effects *and* a duty to provide instructions for safe use.[1]

Shire relies almost entirely on sound bytes which it pulls from the *Stone* and *Weeks* decisions[2] by this Court, to argue that a drug maker has no duty to provide safe instructions. Yet the *Stone* and *Weeks* cases did not address, much less decide, the issue of whether a drug maker has an obligation to provide instructions for safe use.

*Stone* was a failure to warn of side effects case, not an instructions for use case. This Court's purpose in *Stone* was to articulate Alabama's learned intermediary doctrine.

Moreover, the *Stone* Court specifically acknowledged and relied upon the Restatement (Second) of Torts § 402A (1965), comment k, which expresses the twofold nature of a duty to warn as including both warning of side effects *and* "directions" for safe use to mitigate or avoid adverse

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[1] The duty to provide instructions for safe use is reflected in Alabama statute, Ala. Code 6-5-501 which defines a product liability action and specifically includes the term "instructions". Applicable Alabama case law and federal regulations, discussed *infra,* also mandate that a drug maker provide adequate instructions for safe use.

[2] *Stone v. Smith, Kline & French Lab'ys,* 447 So.2d 1301 (Ala. 1984); *Wyeth, Inc. v. Weeks*, 159 So.3d 649 (Ala. 2014) (superseded by statute); *Forest Laboratories, LLC v. Feheley, 296 So.3d 302 (Ala. 2019).*

side effects. *See Stone,* 447 So.2d at 1304 (embracing comment k to § 402A (a product, "accompanied by proper directions and warnings, is not defective…). Thus, *Stone* itself compels an affirmative answer to Question One.

*Weeks* also was not an instructions for use case; indeed, it was not an AEMLD failure to warn case at all, but rather a fraud case. Like *Stone*, *Weeks* actually supports Blackburn's position, not that of Shire. The Court expressly noted the integral "instructions" component of the duty to warn. *See, e.g., Weeks,* 159 So.3d at 694 n. 28 ("[T]his Court has had occasion to express its understanding that the dosage ***instructions and the warnings*** of contraindications and side effects set out in the drug's label make the drug what it is").

The Shire Response also completely ignores the Amicus Curiae Brief of the Alabama Association (the "ALAJ/AAJ Amicus Brief"). This Brief establishes, without challenge by Shire, that every state court throughout the United States that has decided the precise issue posed by Question One regarding safe instructions has held that a drug maker has a separate duty to provide instructions for safe use as well as to warn of side effects.

Shire does not seriously dispute that other categories of manufacturers have the duty to warn of risks of injury and to provide safe instructions for use as well. But Shire suggests without case law support, that there is somehow a "subset" of Alabama product liability cases involving prescription drug makers for which this Court should "carve out" an exception to the established duty to provide instructions for safe use.

To the contrary, Alabama's statutory and common law regarding product liability and the Alabama Extended Manufacturer's Liability Doctrine ("AEMLD")[3] do not differentiate between the obligations of manufacturers of different types of products. Indeed, no Alabama case supports such a "carve out" for prescription drug makers. No public policy or legal doctrine, such as the learned intermediary doctrine, remotely supports holding drug manufacturers to a lesser standard than manufacturers of other products.

Further, as to Question One, Shire makes no argument that applicable FDA regulation 21 C.F.R. § 201.57(c) (the "Safe Instruction

[3] The AEMLD is a judicially created accommodation of Alabama law to the doctrine of strict liability for products. *Keck v. Dryvit Sys. Inc.,* 830 So.1 (Ala. 2002).

Regulation")[4] does not apply to Shire. This Regulation expressly requires a drug manufacturer to provide appropriate instructions for safe use of a prescription drug when laboratory testing is appropriate to avoid or mitigate risk. On its face, the Safe Instruction Regulation is not permissive. The drug maker "must" provide instructions when necessary to avoid or mitigate side effects.

**Question Two:** The applicable case law clearly allows proximate cause to be established by substantial evidence that, had adequate instructions for use been provided by the manufacturer, the plaintiff, or, in the case of prescription drugs, the learned intermediary, would have altered his behavior in a way that would have avoided or mitigated the

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[4] 21 C.F.R. § 201.57(c)(6)(iii) provides:

> This section [of the label] *must* identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation ***and the recommended frequency with which tests should be performed before, during, and after therapy.***

(emphasis added).

plaintiff's injury (such as by following the instructions). [5] In rejecting the same Shire causation argument in the District Court in this action, the Honorable David Proctor explained:

> ***Indeed, proof of proximate cause could take the form of evidence that, although the physician still would have prescribed the drug, the physician would have changed her behavior or treatment in some way that would have resulted in a different outcome for the plaintiff.***

*Blackburn v. Shire,* 2017 WL 1833524, at *8 (N.D.Ala. May 8, 2017) (internal citations omitted; emphasis added citing cases).

Indeed, there is no Alabama case or any other case in the United States holding that, in an instructions for safe use (as opposed to warning of side effects) case, to establish proximate causation, the physician must testify that he or she would not have prescribed the drug even if adequate instructions had been provided.

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[5] Indeed, as explained in more detail in Blackburn's initial brief to this Court, the evidence here shows that the prescribing physician, Dr. Ferrante, and Blackburn both would have followed instructions for specific interval testing. Blackburn's experts, in turn, have opined in detail that if Shire had provided adequate warnings that included adequate instructions for such monitoring of renal function, Blackburn would not have suffered chronic and irreversible kidney injury. *See* Blackburn's initial brief, § III, pp. 2-5; *see also id.* at Exhibit B (containing the even more detailed Statement of Facts from Blackburn's Appellant's Initial Brief to the Eleventh Circuit, both of which are incorporated by reference herein).

Instead, once again, Shire conflates warning of side effects with providing instructions for safe use. But the reason for the requirement, in a failure to warn of side effects case, that the physician must testify that he would not have prescribed the drug if he had been adequately warned of the side effects is clear and straightforward. If the physician was fully aware of the side effects but still would have prescribed the drug, that cuts off the causal connection between the plaintiff's injury and the drug maker's failure to warn of side effects.

Not so with a failure to provide safe instructions case, where causation is cut off only if a physician testifies that he would not have followed the instructions, or otherwise would not have altered his prescribing or treating behavior, so as to mitigate or avoid the plaintiff's injury. The causation analyses between the two types of cases are "apples and oranges".[6]

Thus, to acknowledge the drug maker's duty to provide instructions for safe use, but then to limit an injured plaintiff's ability to establish

[6] The purpose of Alabama's (and the FDA's) requirement that drug manufacturers provide adequate instructions for safe use obviously is so that their drugs *may be used* in the safest and most effective manner possible, not to scare physicians away from prescribing them at all.

proximate cause to proving that his physician would not have prescribed the drug, would be to frustrate the very purpose of the instructions for safe use requirement.

A physician, who unknowingly prescribed a drug with unsafe instructions for use typically would testify that, like Blackburn's physician, Dr. Ferrante, he or she still would have prescribed the drug with safe instructions. A negative answer to Question Two would have the practical effect of giving drug makers such as Shire immunity from liability to Alabama consumers, like Blackburn, who are injured because a prescription drug has inadequate instructions to avoid or mitigate risk.

A negative answer to either Certified Question would leave Alabama as a solitary outlier in the critical area of consumer safety involving prescription drugs.

**The Learned Intermediary Doctrine:** Shire also misapprehends Alabama's learned intermediary doctrine and lack of its relation to the Certified Questions. The learned intermediary doctrine simply holds that a manufacturer's duty to warn runs to the prescribing physician, not to the patient himself. It does not change the nature or

scope of that duty. *See, e.g., Morguson v. 3M Co.*, 857 So.2d 796, 801-02 (Ala. 2003); *Stone, supra*, 447 So.2d at1305.

Nothing in the doctrine suggests that a manufacturer's duty to provide the physician learned intermediary with instructions for safe use is unnecessary or impinges on the physician-patient relationship, as Shire suggests. Rather, the doctrine is merely an affirmative defense to an injured plaintiff's claims but <u>*only*</u> *if* a drug maker first provides the prescribing physician with adequate information, including both warnings of risks *and* instructions for safe use. And adequacy of warnings is a question of fact for the jury. *See State Farm Fire & Cas. Co., v. J.B. Plastics*, 505 So.2d 1223, 1227 (Ala. 1987).

## II. LEGAL ARGUMENT IN REPLY

### A. Question One

*Consistent with the Learned Intermediary Doctrine, may a pharmaceutical company's duty to warn include a duty to provide instructions about how to mitigate warned-of risks?*

#### 1. <u>*Stone* And *Weeks* Do Not Support Shire's Position On Question One.</u>

Shire relies almost exclusively in its Response to Question One on this Court's decisions in *Stone* and *Weeks, supra* at n. 2, but those cases are wholly inapplicable.

*Stone v. Smith, Kline & French Lab'ys*, 447 So.2d 1301, 1304 (Ala. 1984), involved certified questions of Alabama law in connection with a drug manufacturer's alleged failure to provide any warning at all about a side effect of its drug, cholestatic jaundice, not the failure to provide adequate instructions for safe use that would avoid or mitigate that side effect.

The *Stone* decision simply established that, consistent with comment k, in the case of an "unavoidably unsafe and properly prepared prescription drug", the adequacy of accompanying warnings and directions determine whether a product is defective or unreasonably dangerous, and that adequate warning to the prescribing physician, (not to the patient), is sufficient as a matter of law.

In other words, the *Stone* Court adopted the learned intermediary doctrine in Alabama. *Stone,* 447 So.2d at 1304. It did **not** alter the twofold nature of the duty to warn or declare that, in Alabama, prescription drug manufacturers alone, unlike manufacturers of every other type of product, need not provide adequate instructions for safe use of their drug products. *Id.*

To the contrary, this Court in *Stone* specifically approved the Restatement (Second) of Torts § 402A (1965), comment k, which expresses the twofold nature of a duty to warn as including both warning of side effects *and* "directions" for safe use to mitigate or avoid adverse side effects. *See Stone,* 447 So.2d at 1304 (embracing comment k to § 402A, titled "[d]irections or warning").

Comment k to § 402A provides that prescription drugs are considered defective only if they are not "accompanied by proper *directions and* warning". Restat. (2d) of Torts §402A cmt. k (emphasis added). Citing comment k, this Court concluded in *Stone* that "the adequacy of warnings issued by a drug manufacturer", as expressed in §402A and its comments which include the adequacy of directions, "bears on whether a plaintiff has proved a prima facie case under the Alabama Extended Manufacturer's Liability Doctrine". *Stone,* 447 So.2d at 1304; *see also, e.g., Stafford v. Nipp,* 502 So.2d 701, 705 (Ala. 1987) (in which this Court also recognized the twofold nature of the duty to warn in holding that the plaintiff created a fact issue as to whether the defendant

"failed to warn ***or instruct*** [the plaintiff] concerning the taking of prescription drugs over a long period of time") (emphasis added).[7]

Thus, rather than supporting Shire's attempt to limit a drug manufacturer's duty to warning about side effects only, *Stone* actually demonstrates that, consistent with the Restatement, Alabama law imposes a twofold duty on manufacturers, including, specifically, prescription drug manufacturers, both to warn of side effects and to provide instructions for the safe use of their products.

*Wyeth, Inc. v. Weeks,* 159 So.3d 649 (Ala. 2014) (superseded by statute as stated in *Forest Laboratories, L.L.C. v. Feheley*, 295 So.3d 302 (Ala. 2019), also supports Blackburn, not Shire. The issue in *Weeks* was whether a brand name manufacturer could be held liable for misrepresentation or fraud under Ala. Code. (1975) § 6-5-101 for statements it made in connection with the manufacture of a drug in a lawsuit brought by a consumer allegedly injured by the *generic* version of that drug. *Weeks,* 159 So.3d at 656.

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[7] The ALAJ/AAJ Amicus Brief at § I of its Argument contains an excellent explanation of how Alabama's AEMLD is consistent with the Restatements Second and Third in this regard, as well as in step with the overwhelming national consensus. Shire is utterly silent in its Response to the compelling authority included therein.

*Weeks* was not an AEMLD case and did not address an AEMLD failure to warn claim based on the instructions for safe use. *Weeks,* 159 So.3d at 656. ("[F]or purposes of this certified question, we will not treat the Weeks' claims as AEMLD claims governed by the principles of the AEMLD."); *accord Russell v. Ethicon, Inc.*, 2020 WL 4732106, at *6 (N.D.Ala. 2020)( "But *Wyeth* [*v. Weeks*] was not about either negligence or the AEMLD; it was a case about fraudulent misrepresentation."). Indeed, this Court specifically concluded that the plaintiffs' claim in *Weeks* was not "in substance a products-liability claim" at all. *Id.* at 658. Therefore, *Weeks* has no application or precedential value regarding a determination of the AEMLD duty to warn presented by Question One.

Moreover, this Court itself acknowledged in *Weeks* the integral "instructions" component of the duty to warn: "[T]his Court has had occasion to express its understanding that the dosage ***instructions and the warnings*** of contraindications and side effects set out in the drug's label make the drug what it is.*" Weeks,* 159 So.3d at 694 n. 28 (emphasis added; citing *Stone, supra*, 447 So.2d at 1304); *see also id.* at n. 27 (referring to the necessity of providing "**instructions and warnings**" on drug labels) (emphasis added); *Id.* at 695 n. 28 (quoting the United States

Supreme Court, citing the Restatement (3d) of Torts: Products Liability § 2(c): "A failure-to-warn claim alleges that a product is defective when the foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of reasonable ***instructions or warnings*** by the seller or other distributor…and the omission of the ***instructions or warnings*** renders the product not reasonably safe") (emphasis in the original; internal quotation marks omitted).[8] *Id.* at n. 28.

Shire cites the Court's reference in *Weeks* to language from an Eleventh Circuit opinion, *Toole v. Baxter Healthcare Corp.,* 235 F.3d 1307, 1313-14 (11th Cir. 2000), specifically, that a manufacturer's duty "is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the use of its product". But, in *Toole,* the Eleventh Circuit *affirmed* a jury verdict in favor of an injured

[8] Justice Shaw, concurring specially, stated that the brand name drug manufacturer could be liable for failure to provide "important facts to Danny Weeks's doctor ***about how metoclopramide is to be taken properly***", and "knew that its [inadequate] ***instructions on the use of metoclopramide*** would be repeated by the generic-drug companies" and cause harm) (emphasis supplied).

plaintiff against a breast implant manufacturer, based upon the following legal principle:

> [T]his obligation of a manufacturer to give appropriate warnings of things that would not be appreciated by the consumer may be discharged by giving appropriate warnings to the physicians who are going to be using the product, taking into account the type of knowledge that one would expect physicians to have as a result of their professional training and experience, ***and providing them with additional information, supplemental information, that would help those physicians to assess the proper use of that product*** and to understand the types of risks, if any, that would be associated with that.

*Toole,* 235 F.3d at 1314 (emphasis added).

Here, information regarding specific interval testing necessary to monitor, and thereby to avoid or mitigate, the adverse renal effects of Lialda is just the sort of "additional information" that would have helped Dr. Ferrante "assess the proper use of that product" and thereby avoid Blackburn's permanent kidney injury. Thus, *Weeks* clearly supports, indeed requires, an affirmative answer to Question One. [9]

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[9] In addition, *Stone* and *Weeks* both included citations to the Fifth Circuit's decision in *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir. 1974), which Shire cites repeatedly in its Response. [Response Brief at 23-25].

*Reyes* like *Stone*, involved a failure to warn about side effects, not a failure to provide instructions for use. *Id.* Most striking, the Fifth Circuit

Shire ignores other Alabama authority that requires an affirmative answer to Question One. This Court judicially created the AEMLD in *Casrell v. Altec Industries, Inc.,* 335 So.2d 134 (Ala. 1976) and *Atkins v. American Motors Corp.,* 335 So.2d 134 (Ala. 1976). In *Atkins,* the Court specifically referred to comments j and k of § 402A when it discussed the retention under the AEMLD of certain defenses such as assumption of the risk. *Atkins,* 335 So.2d at 143 (stating that adequate warnings include "*directions and* warning" as explained in those comments) (emphasis added).

And this Court has continued to rely on comments j[10] and k to § 402A as a "blueprint for the liability of drug manufacturers". *Stone, supra*, 447 So.2d at 1303 n. 2 (citing *Casrell* and *Atkins, supra*); *see also*

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in *Reyes* also embraced comment k of Restatement (2d) of Torts § 402A as a proper statement of Texas law on a drug or vaccine manufacturer's duty to warn as including a duty to provide both "*directions and* warning". *Id.* at 1274 (emphasis added). Thus, *Reyes* also supports *Blackburn,* not Shire.

[10] Specifically, comment j of the Restatement's § 402A states: "In order to prevent the product from being unreasonably dangerous, the seller may be required to give *directions* or warning, on the container, *as to its use*." Restat. (2d) of Torts §402A cmt. j (emphasis added). For "poisonous drugs", comment j further states that a "warning as to use may be required." *Id.* (emphasis added).

*Griggs v. Combe, Inc.,* 456 So.2d 790, 792 (Ala. 1984); Ex Parte *Chevron Chem. Co.,* 720 So.2d at 927 (Ala. 1988).

Indeed, this Court has already concluded that the "standards for warnings" under the AEMLD are the *same* as those of § 402A of the Restatement (2d) of Torts and negligent failure to warn, *i.e.,* include "directions and warning". *Chevron,* 720 So.2d at 929. Thus, this Court actually has recognized the dual nature of a manufacturer's dual duty to war -- both of side effects and to provide instructions for safe use-- for almost half a century.

The Court's embrace of the twofold nature of a manufacturer's duty to warn is also consistent with the Alabama Legislature's definition of a products liability action as including injury caused by "instructions". *See* Ala. Code (1975) §§ 6-5-501 and 6-5-521(a).

2. FDA Regulations Require Safe Instructions For Use.

Shire has not pointed to a single case *in any jurisdiction* that holds that a drug manufacturer need not provide instructions for safe use of its product. To the contrary, states across the country uniformly impose the

same duty to provide instructions for use on drug manufacturers as they do manufacturers of other consumer products. [11]

What is more, FDA regulations *expressly require* prescription drug manufacturers to provide instructions for safe use in their drug labeling. *See, e.g.,* 21 C.F.R. § 201.57(c). As noted, *supra*, this Safe Instruction Regulation is mandatory. The drug maker must not only identify helpful laboratory tests, but must also provide information regarding "the recommended frequency" of such tests. The factual issue in this case is whether Shire's instruction regarding "periodic" testing was adequate or safe.[12]

The FDA prescription drug labeling regulations provide a mandatory, minimum "floor" for drug manufacturers' warnings, that may be supplemented by state laws that are stronger, but which may not be

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[11] *See, e.g.,* the detailed jurisdictional survey contained in the ALAJ/AAJ Amicus Brief at § I (C), demonstrated the widespread acceptance of drug manufacturers' obligation to provide instructions, which Shire studiously avoids.

[12] Shire cites *PLIVA v. Mensing* only in connection with its flawed preemption argument, while ignoring the United States Supreme Court's acknowledgement therein of a drug maker's duty to provide instructions. [Shire Response Brief at 40]

reduced. *See, e.g., Wyeth v. Levine*, 555 U.S. 555, 573-74 (U.S. 2009). Answering "no" to Question One, as Shire suggests, would not only fall below FDA's minimum standards for drug labeling, it would directly contravene and frustrate them. This is the basis for Blackburn's preemption argument. Shire's silence on the FDA requirements regarding instructions for safe use is deafening.

3. The Learned Intermediary Doctrine Has No Application To Question One.

Alabama's learned intermediary doctrine merely provides that a drug manufacturer's duty to warn runs to the prescribing physician, not the ultimate user, and that *adequate* warnings and instructions in the drug label are an affirmative defense. The doctrine **does not** encompass the separate and distinct issue posed by the Question One regarding whether the maker has a duty to provide instructions for use.

Shire cites multiple inapposite cases involving pharmacists, as opposed to drug manufacturers, to support its assertion that "this Court repeatedly has declined to force a prescription drug manufacturer by judicial fiat to intrude upon the physician-patient relationship". [Shire Response Brief at 16]. But cases describing pharmacists' duties to warn have no bearing on the scope of prescription drug manufacturers' duties.

This is because manufacturers are uniquely responsible for the contents of their drug labels and warnings. *See, e.g., In re Chantix*, 881 F.Supp. 2d 1333, 1338-39 (N.D.Ala. 2012) ("[A] manufacturer bears responsibility for the contents of its label at all times.") (quoting *Wyeth v. Levine*, 555 U.S. 555, 570-71 (U.S. 2009).

Among other things, drug manufacturers are responsible for both "crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Wyeth*, 555 U.S. at 570 (citing 21 CFR § 201.80(e) (requiring a manufacturer to revise its label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"); § 314.80(b) (placing responsibility for post marketing surveillance on the manufacturer); 73 Fed. Reg. 49605 ("Manufacturers continue to have a responsibility under Federal law ... to maintain their labeling and update the labeling with new safety information")).

Obviously, pharmacists have no such responsibility for the adequacy of a drug maker's label. Drug makers' unique responsibility alone renders the pharmacist cases cited by Shire inapplicable, but so do the following details of those cases.

Shire pulls a single sound byte from *In re Chantix (Varenicline) Prods. Liab. Litig.,* 881 F.Supp.2d 1333, 1342 n. 2 (N.D. Ala. 2012), about a physician's medical judgment (incorrectly cited as footnote 2, which actually discusses FDA's premarket approval and CBE mechanism, not physician's judgment). However, *In re Chantix* quoted with favor the Restatement (Third) of Torts: Products Liability, which expressly provides that a product may be defective due to "inadequate instructions or warnings…provided to prescribing and other healthcare providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings". Rest. (3d) of Torts: Products Liability §6(b); (d)(1).

*In re Meridia Prod. Liab. Litig.*, 328 F.Supp.2d 791 (N.D. Ohio 2004), actually supports an affirmative answer to Question One, because it acknowledges the twofold nature of a drug manufacturer's duty to warn as including a duty to provide instructions for use: "[T]he Court must examine both defendants' warnings ***and their instructions*** and assess

the adequacy of each. *In re Meridia,* 328 F.Supp.2d at 811 (emphasis added).[13]

For all these reasons, the answer to Question One should be "yes."

### B. Question Two

> *May a plaintiff establish that a failure to warn caused his injuries by showing that his doctor would have adopted a different course of testing or mitigation, even though he would have prescribed the same drug?*

First, a negative answer to Question Two is irreconcilably inconsistent with the obvious purpose of safe instructions, which is to allow a physician to safely prescribe a drug while avoiding or mitigating the risk of side effects.

Shire asks the Court to establish as a tenet of Alabama law the following: A plaintiff in Alabama who proves (1) that, if adequate instructions had been provided, both he and his treating physician would have followed them, and (2) that following such adequate instructions would have avoided or mitigated his injury, is nonetheless *barred from*

[13]*See also Meridia id.* at 811 ("Under the learned intermediary doctrine, manufacturers of prescription drugs escape liability for failure ***to instruct*** and warn consumers so long as they ***adequately instruct*** and warn physicians responsible for prescribing medication.").

*any recovery under the AEMLD merely because his physician testifies that he still would have prescribed the drug.*

Such a holding would create practical immunity for drug manufacturers in the State, because typically no physician would testify that, although he unknowingly prescribed the drug to his patient with unsafe instructions, he would not have done so if the instructions had been safe and adequate

Indeed, Shire can cite no *instructions for use* case in Alabama or elsewhere that supports answering Question Two in the negative. Shire once again relies on inapplicable failure to provide *warnings of side effects* cases, and refuses to recognize the distinction between the two aspects of a manufacturer's duty, or the differing causal analyses required by this distinction.

1. Alabama Law of Proximate Cause Supports an Affirmative Answer to Question Two.

Many decisions by this Court cited in Blackburn's Initial Brief hold that proximate cause in an inadequate instructions case may be established by substantial evidence that an adequate instruction would have been followed, and the injury or harm thereby would have been mitigated or avoided. *See, e.g., Morguson v. 3M,* 857 So.2d 796, 800 (Ala.

2003); *Sears, Roebuck and Co. v. Harris,* 630 So.2d 1018, 1030 (Ala. 1993); *Gurley v. American Honda Motor Co., Inc.,* 505 So.2d 358, 361 (Ala. 1987); *Deere & Co. v. Grose,* 586 So.2d 196, 198 (Ala. 1981). See also *Hicks v. Commercial Union Insurance Co., 651 216, 217 (Ala. 1994)* (expert testimony presented fact issue as to whether manufacturer gave adequate "instruction" for use of pipe stoppers).

Other courts applying Alabama law have likewise acknowledged that when a drug maker fails to provide adequate instructions for use cases, proximate cause may be established by substantial evidence that, while the learned intermediary still may have prescribed the drug, he would have altered his prescribing or treating behavior in some way that would have mitigated or avoided the plaintiff's injury. *See, e.g., Barnhill v. Teva Pharmaceuticals USA, Inc.,* 819 F.Supp.2d 1254, 1261 (S.D.Ala. 2011) (proximate cause may be demonstrated by evidence that, though the learned intermediary still would have prescribed the drug, she would have altered her treatment behavior "in some way that would have resulted in that would have resulted in a different outcome for the Plaintiff"); *Blackburn v. Shire,* 2017 WL 1833524, at *8 (N.D.Ala. May 8, 2017) (same; citing *Barnhill*); *Fields v. Eli Lilly & Co.,* 116 F.Supp.3d

195, 1307 (M.D.Ala. 2015) (same); *Toole v. McClintock,* 999 F.2d 1430, 1433 (11th Cir. 1993) (proximate cause may be established if warnings or instructions from the manufacturer would have caused the treating physician to "behave differently").

Alabama law on this point again is in lockstep with the law of every other jurisdiction having had occasion to address this proximate cause issue. For example, *Bee v. Novartis Pharmacy* [14] discussed many jurisdictions' holdings that, even where a physician continues prescribing a drug with knowledge of a particular risk of a side effect, evidence that adequate instructions for use would have caused "changes to that doctor's prescription or treatment procedures will generate triable questions of fact on the question of causation."

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[14] 18 F.Supp.3d 268, 294-95 (E.D. N.Y. 2014) (citing *Georges v. Novartis Pharm. Corp.,* 2012 WL 9083365, at *5-6 (C.D.Cal. Nov. 2, 2012); In *re Aredia & Zometa Prods. Liab. Litig.,* 2010 WL 5092784, at *2 (M.D.Tenn. Dec. 7, 2010); *re Aredia & Zometa Prods. Liab. Litig.,* 2009 WL 2497692, at *3 (M.D. Tenn. Aug. 13, 2009) ("[I]t is sufficient for Plaintiff to survive summary judgment to show that one of [his] treating physicians…would have behaved differently."); *In re Aredia & Zometa Prods. Liab. Litig.,* 2009 WL 2496843, at *2 (M.D. Tenn. Aug. 13, 2009) (sufficient to survive summary judgment on causation to present evidence the actions of the treating physician would have "been different")).

Another district court noted the overwhelming number of courts holding that proximate cause may be established by evidence that the treating physician simply would have behaved differently, such that the injury would have been avoided. It found "the exhaustive line of judicial precedent to be persuasive here". *Georges v. Novartis Pharmaceutical,* 2012 WL 9083365, at *5-6 (C.D. Cal. 2012); *see also, e.g., Holley v. Gilead Sciences, Inc.,* 379 F.Supp.3d 809, 830 (N.D. Cal. 2019) [15] ("[C]ourts have found triable issues of causation where plaintiffs have presented evidence that their physicians would have used monitoring tests if adequately warned or that they would have altered their prescription practices in a way that may have prevented injury.") (citing *In re Xarelto (Rivaroxaban) Prods. Liab. Lit,* 2017 WL 1393480, at *2-3 (E.D.La. Apr. 17, 2017) (denying summary judgment where the plaintiff "would have used [monitoring tests] had they been adequately instructed to do so", and thereby avoided "significant medical issues")).

[15] *Gilead* involved monitoring patient kidney function to catch early signs of acute injury before that injury becomes chronic, because patients are generally asymptomatic during the early stages. *Id* at 815. This case presents the same situation.

Shire relies exclusively on this Court's decision in *Weeks* to argue that the foregoing authorities have somehow been abrogated. But they have not, and *Weeks* did not create the exception to existing law of proximate cause that Shire posits. Indeed, it is no more applicable to a proper resolution to Question Two than it was for Question One.

Again, as the Blackburn District Court explained in rejecting the very same argument by Shire at the inception of this case:

> ***Indeed, proof of proximate cause could take the form of evidence that, although the physician still would have prescribed the drug, the physician would have changed her behavior or treatment in some way that would have resulted in a different outcome for the plaintiff.***

*Blackburn v. Shire,* 2017 WL 1833524, at *8 (N.D.Ala. May 8, 2017) (internal citations omitted; emphasis added).

The Eleventh Circuit, too, acknowledged the persuasiveness of the District Court's reasoning in its *Blackburn* opinion, regarding proximate cause. The Eleventh Circuit stated that it has "arguably approved of this theory under Alabama law", but seeks clarity from this Court because of Shire's distortion of *Weeks*. *Blackburn v. Shire*, 18 F. 4th 1310, 1322 (11th Cir. 2021) (citing *Toole, supra,* 999 F2d at 1433). Blackburn's

comprehensive discussion of *Weeks* and *Stone* makes clear that an affirmative answer to Question Two is appropriate.

2. Shire's Proximate Cause Cases are Inapplicable.

Other than *Weeks* and *Stone*, which are distinguishable for reasons stated, Shire simply pulls sound bytes from other Alabama cases that do not involve prescription drug manufacturers at all.

For instance, this Court's decision in *Shades Ridge Holding Co., Inc. v. Cobbs, Allen & Hall Mortg. Co., Inc.,* 390 So.2d 601, 606-07 (Ala. 1980), was a construction mortgage dispute. Moreover, the Court therein *reversed* the trial court's judgment in favor of the defendant on the issue of proximate cause, because the trial court erred in failing to consider the issue i*n the context of the specific tort at issue. Shades Ridge Holding.,* 390 So.2d at 611-612 ("Causal concepts should be used flexibly in order to serve adequately the underlying policy considerations regarding the various tort actions").

*Rondini v. Bunn,* 2021 WL 1939171, at *5 (Ala. May 7, 2021), involved wrongful death claims against an assailant resulting from the suicide of his sexual assault victim. The Court answered the discrete certified question of whether the suicide of a victim of sexual assault is a

superseding cause that would absolve an assailant of liability in the negative. It, too, is inapplicable and does not address the proximate cause question presented here.

*Deere & Co. v. Grose*, 586 So.2d 196, 198 (Ala. 1991), was a tractor injury case, which Shire cites for the correct proposition that a plaintiff must show that, if proper warnings or instructions had been given, the injury would have been avoided.[16] But the case directly undermines Shire's position on both Questions, as it involved an AEMLD claim *based on the instructions for safe* use of the defendant manufacturer's product, the inadequacy of which allegedly *caused the plaintiff's injury.* This Court held that Plaintiff's claim was properly, and successfully, submitted to a jury. *Grose,* 586 So.2d at 198-99.

Shire devotes three pages of its Response to the Fifth Circuit's decision, under Louisiana law, *In re Taxotere (Docetaxel) Prods. Liab. Litig.,* 994 F.3d 704, 708-09 (5th Cir. 2021). [Shire Response Brief, at pp.

[16] This is precisely what the evidence demonstrates here--- had Shire included the specific interval testing instructions which it knew were necessary to avoid Blackburn's permanent kidney injury, Dr. Ferrante would have followed those instructions, and his permanent kidney injury would have been avoided.

55-57] But that case again involved a drug manufacturer's failure to warn of side effects, *not* its failure to provide instructions for safe use. *In re Taxotere,* 994 F.3d at 706-707.

3. The Learned Intermediary Doctrine has No Application to Question Two.

Again, the learned intermediary doctrine provides that a drug manufacturer's duty to warn runs to the treating or prescribing physician, not to the patient himself. *See, e.g., Morguson v. 3M Co.*, 857 So.2d 796, 801-02 (Ala. 2003); *Stone, supra*, 447 So.2d at 1305; *see also Toole v. McClintock*, 999 F.2d 1430, 1433 (11th Cir. 1993) ("Under the learned intermediary doctrine the adequacy of [a prescription drug manufacturer's] warning is measured by its effect on the physician… to whom it owed a duty, and not by its effect on the [ultimate consumer].") (citation and internal quotation marks omitted).

Shire relies only on cases that addressed whether a manufacturer's drug label warned of a particular side effect. On the issue of proximate cause, those cases are unique to warnings of side effects cases because, if the prescribing doctor fully knew of the risk and decided to still prescribe the drug, the warning would not have "prevented the accident." *See Deere & Co. v. Grose*, 586 So.2d 196, 198 (Ala. 1991).

Instructions for safe use, however, are different in that they generally provide direction on how to minimize risk while using *this* product. *See, e.g.*, DAVID G. OWEN, PRODUCTS LIABILITY LAW, 558-59 (4th ed. 2022). In cases like this one where the prescribing doctor would have read and followed adequate instructions, evidence supports causation in that the doctor's different acts would have "prevented the accident." *See Grose*, 586 So.2d at 198.

For example, the Court addressed causation involving a failure to provide adequate instructions in *Sears, Roebuck & Co. v. Harris*, 630 So. 2d 1018, 1029 (Ala. 1993). That case involved several people that either died or were injured by carbon monoxide poisoning due to a defective water heater. *Id.* at 1022. One of the plaintiff's experts testified that the labeling failed to warn of the dangers of carbon monoxide and "failed to instruct users to vent the water heater and to connect it to natural gas, and not LP gas." *Id.* at 1024. The Court reasoned that the plaintiff testified that he read "all the existing labels" and the fact that he "followed the directions for lighting the pilot light included on the operating instructions label also created an inference that he would have

followed additional instructions and warnings." (emphasis added) *Id.* at 1030. The same proximate cause rationale is directly applicable here.

Therefore, the Court's affirmative answer to Question Two would align with the learned intermediary doctrine and universally recognized proximate cause standards in drug cases involving unsafe instructions.

### C. The Miscellaneous "Straw Man" Arguments

The remaining Shire "straw man" arguments are no more compelling or on point.

*Stare decisis:* Shire appeals to the doctrine of stare decisis. In fact, it is Shire that is trying to "rewrite" and avoid established Alabama products liability law governing a manufacturer's duty to provide instructions for safe use and regarding proof of proximate cause.

*The American College of Gastroenterology Clinical Practice Guidelines:* Plaintiff's experts disagree with these Guidelines. This is a battle of experts which has no bearing on either Certified Question.

*"Recommendations" vs. Instructions:* Shire posits a semantic argument regarding the purported difference between "recommendations" and "instructions" that is also unrelated and unhelpful to the inquiries at hand.

State law and federal regulation require instructions for safe use. Recommendations for laboratory testing to avoid or mitigate side effects, which are mandatory under the Safe Use Instruction, are facially encompassed by the concept of instructions.

The Fifth Circuit has held that a drug manufacturer's duty to warn included "recommended medical monitoring schemes—*which are, in essence, instructions for safe use of prescription drugs*." *Stahl v. Novartis Pharms. Corp.*, 283 F.3d 254, 269-70 (5th Cir. 2002) (applying Louisiana law) (emphasis added). Thus, Shire is making a "distinction without a difference."

*The FDA Regulatory Framework:* Shire spends extensive time discussing history of FDA approval of Lialda. As the Supreme Court made clear, FDA approval of a drug label does not preclude a state law product liability claim. *Wyeth v. Levine*, 555 U.S. 555 (2009). Prior FDA approval has nothing to do with either of the Certified Questions.

*Preemption and the Supremacy Clause:* Shire asks this Court to impermissibly disregard the Safe Instruction Regulation. Shire's claim that it has no duty to provide instructions for safe use is preempted because it is inconsistent with the "floor" established by the Safe

Instruction Regulation based upon preemptive principles enunciated in *Wyeth v. Levine*.

*Affirmative answers to the certified questions would not interfere with the Physician-Patient relationship:* Shire and the DRI Amicus Brief suggest that an affirmative answer to the Certified Questions would somehow interfere with the physician-patient relationship or involve Shire in the practice of medicine. Both suggestions are a further distraction. As explained, *supra*, the purpose of requiring a drug maker to provide safe instructions is to enhance, not interfere with, the physician's ability to safely prescribe drugs. Further, the drug maker's responsibility for the label is clearly established by the United States Supreme Court in *Wyeth v. Levine* and a legion of other cases. To say that a drug maker must provide a safe label has nothing to do with somehow interfering with the physician-patient relationship or involving a drug maker in making medical decisions regarding an individual patient.

## III. CONCLUSION

To answer either Certified Question in the negative would be to "carve out" a completely unwarranted exception to drug makers' duties and to foreclose the ability of Alabama plaintiffs to establish liability and

causation based on a drug maker's failure to provide safe instructions for use. It would also render Alabama completely out of step with the products liability jurisprudence of every other jurisdiction in this country.

Moreover, such flawed interpretations of the duty to provide safe instructions and regarding proximate cause would directly undermine the very purpose of Alabama's learned intermediary doctrine which is to incentivize drug manufacturers to fully inform physicians, so as to enable the treating physician to safely and effectively treat patients with prescription drug products.

WHEREFORE, Appellant Blackburn respectfully requests the Court to answer Questions One and Two in the affirmative.

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## CERTIFICATE OF COMPLIANCE

Undersigned counsel certifies that this brief complies with the font and word limitations set forth in Ala. R. App. P. 28 and 32. The type used is Century Schoolbook 14. This brief contains 6849 words.

*/s/Jonathan H. Waller*
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## CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on May 5, 2022, I electronically filed a true copy of **Plaintiff-Appellant's Blackburn's Reply to Defendant Shire's Response to Certified Questions** with the Clerk of the Alabama Supreme Court via its electronic filing system and served the document by electronic mail to the following:

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