APPENDIX

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Appendix A

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

No. 20-12258

MARK BLACKBURN,

Plaintiff-Appellant,

v.

SHIRE U.S., INC., SHIRE, LLC,

Defendants-Appellees.

SHIRE DEVELOPMENT, LLC, et al.,

Defendants.

Filed: Nov. 7, 2022

Before JILL PRYOR, LUCK, and BRASHER,
Circuit Judges.

OPINION

BRASHER, Circuit Judge:

This appeal returns to us after the Supreme Court of Alabama answered two questions we certified for its review. *See Blackburn v. Shire U.S., Inc.*, 18 F.4th 1310, 1322 (11th Cir. 2021), *certified question answered sub nom. Blackburn v. Shire U.S., Inc.*, No. 1210140, --- So. 3d --- (Ala. Sept. 30, 2022).

As we explained in our previous opinion, Mark Blackburn was diagnosed with advanced-stage kidney disease after taking LIALDA, a drug manufactured by Shire Pharmaceuticals, to treat Crohn's disease. Blackburn attributes his injuries to inadequacies in LIALDA's warning label. Blackburn does not contend that Shire failed to warn of the risk of kidney disease. Instead, he contends that if the LIALDA label had more explicitly instructed doctors to monitor patients' kidney function, his physician would have treated him differently, discovered this side effect, and instructed him to stop taking LIALDA.

The district court granted summary judgment to Shire. Although it concluded that Alabama law supported Blackburn's failure- to-warn theory, the district court also concluded that Blackburn could not demonstrate a causal link between his injuries and the label's shortcomings because Blackburn's physician did not read the LIALDA label before prescribing the drug.

We disagreed with the district court. We held that issues of disputed fact should have prevented summary judgment. *See Blackburn*, 18 F.4th at 1319-21. But we asked the Supreme Court of Alabama to tell us whether Blackburn's failure-to-warn claim was viable under Alabama law. *Id.* at 1321-22. Specifically, we asked the Supreme Court of Alabama to answer the following two questions:

> (1) 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?

> (2) 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?

Id. at 1321.

The Supreme Court of Alabama has answered both questions "yes." *See Blackburn v. Shire U.S., Inc.*, No. 1210140, --- So. 3d --- (Ala. Sept. 30, 2022). In the words of the Supreme Court of Alabama, a failure-to-warn claim under Alabama law "may include allegations of inadequate instructions about how to mitigate warned-of risks." *Id.*, slip op. at 26. And "it follows that a plaintiff may establish causation by showing that his or her physician would have adopted a different course of testing or mitigation, even though the physician would have prescribed the same drug." *Id.* Accordingly, Alabama law recognizes Blackburn's cause of action.

There is only one remaining question: whether federal law preempts this state-law cause of action. We expressly reserved this issue in our previous opinion. *See Blackburn*, 18 F.4th at 1319 n.1. And, because of the Supreme Court of Alabama's answers to our certified questions, we must answer it now.

The Supremacy Clause establishes that federal law "shall be the supreme Law of the Land ... any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. "Where state and federal law directly conflict, state law must give way." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 617 (2011) (quotation omitted). A direct conflict exists, and state law is preempted, when it is

"impossible for a private party to comply with both state and federal requirements." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019) (quotations and citations omitted); *see Wyeth v. Levine*, 555 U.S. 555, 571 (2009). "[T]he possibility of impossibility is not enough." *Albrecht*, 139 S. Ct. at 1683 (Thomas, J., concurring) (cleaned up).

For a medication to be lawful, the Food and Drug Administration must approve its label. 21 U.S.C. §§ 355(a), 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i) (2016). The label must disclose, among other things, warnings and precautions related to the drug's effects. *See* 21 C.F.R. § 201.56(d)(1) (2015). Once a label is approved, the manufacturer is generally not permitted to alter it without the Administration's approval. The "default rule" is that substantive changes to a drug's label must go through the Administration. *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 806 (7th Cir. 2018); 21 C.F.R. § 314.70(b)(2)(v)(A) (2016). However, under the changes-being-effected regulation, a manufacturer can make certain changes to its label without prior approval. 21 C.F.R. § 314.70(c)(6)(iii) (2016). During this process, manufacturers need not wait for the Administration's preapproval; instead, they can file a supplemental application with the Administration. *Wyeth*, 555 U.S. at 568; 21 C.F.R. § 314.70(c)(6) (2016). Through this process, a manufacturer may "add or strengthen a contraindication, warning, [or] precaution," 21 C.F.R. § 314.70(c)(6)(iii)(A) (2016), or "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," *id.* § 314.70(c)(6)(iii)(C). Language added through the changes-being-effected

process must be in response to "'newly acquired information' about the 'evidence of a causal association' between the drug and a risk of harm." *Albrecht*, 139 S. Ct. at 1673 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). "Newly acquired information" is defined as "data, analyses, or other information not previously submitted to the agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data ...." 21 C.F.R. § 314.3(b) (2016).

Because the "changes-being-effected" regulation permits label changes, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Albrecht*, 139 S. Ct. at 1679. Impossibility preemption exists only where there is "clear evidence that the FDA would not have approved a change." *Wyeth*, 555 U.S. at 571. Whether "clear evidence" exists is a "matter of law for the judge to decide." *Albrecht*, 139 S. Ct. at 1679. The Administration's actions can affect the answer to the pre-emption question. *Id.* Nevertheless, manufacturers "cannot propose a change that is not based on reasonable evidence." *Id.* (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)).

Shire contends that it could not have supported a label change with newly acquired information, or, at the least, Blackburn failed to identify any. This argument is belied by the record. Benjamin England, a regulatory expert retained by Blackburn, testified that Shire could have changed the label to include a stronger monitoring instruction. His expert report

noted that sufficient evidence, including "a growing body of medical literature," supported a stronger monitoring instruction. England also identified reports of renal impairment that Shire received between the label's initial approval and Blackburn's injury. He concluded that sufficient evidence would have led to a label change, had Shire sought one. England further opined that the Administration would have approved a label change based on adverse event reports and medical literature available to Shire after the label's initial approval. For example, an article from 2009 recommended the monthly monitoring schedule that Blackburn asserts should have been part of Shire's warning.

Our review is circumscribed by the standard for summary judgment. Taking England's testimony in Blackburn's favor as we must, we cannot say that Blackburn's claim is preempted. The regulations' broad definition of newly acquired information includes the sources England relied on. 21 C.F.R. § 314.3(b) (2016). We therefore conclude that the record contains examples of information available to Shire that could have formed the basis for seeking a label change.

Moreover, the Administration never indicated that it would not have accepted the change. Shire seemingly contends that the Administration already rejected the change, but its argument is not persuasive. It suggests that the evidence of mesalamine products' impact on renal function is so pervasive that the Administration must have determined that Blackburn's suggested label change was inappropriate. It notes that the "long history of

human experience with mesalamine-containing products" reveals that the Administration knew of the risk before LIALDA was approved. But Shire does not contend that it ever attempted to strengthen the monitoring instruction. The changes-being-effected regulation places the onus on the manufacturer to "ensur[e] that its warnings remain adequate as long as the drug is on the market." *Wyeth*, 555 U.S. at 570-71 (rejecting an argument that would shift "primary responsibility [over] drug labeling" to the Administration). Importantly, between LIALDA's initial approval in 2007 and Blackburn's prescription in 2013, the label changed in only one significant way: the Administration "request[ed]" that Shire add "renal failure" to the warnings section of the label. This change suggests that the Administration may have been inclined to accept a stronger monitoring instruction, had Shire offered it.

We further reject Shire's alternative argument that it was precluded from changing the warning because it was contained in the "Highlights" section of the LIALDA label. *See* 21 C.F.R. § 314.70(b)(2)(v)(C) (2016). The relevant regulation states that "[a] supplement must be submitted for" three categories of "labeling changes." *Id.* §§ 314.70(b)(1), (b)(2)(v). Shire focuses on subsection (b)(2)(v)(C), which requires a supplement for "[a]ny change to the information required by" the Highlights section, 21 C.F.R. § 201.57(a). But Shire overlooks subsection (b)(2)(v)(A), which exempts "[c]hanges in labeling ... described in paragraph[] (c)(6)(iii)." *Id.* § 314.70(b)(2)(v)(A). Subsection (c)(6)(iii), of course, is the very subsection at issue here, regarding "changes-being-effected." And one of the categories in the

"changes-being-effected" regulation permits "add[ing] or strengthen[ing] an instruction about dosage and administration that is intended to increase the safe use of the drug product." *Id.* § 314.70(c)(6)(iii)(C). Blackburn's proposed language fits into that category because it is a recommendation for how to administer LIALDA in a way that increases its safe use.

On this summary judgment record, we cannot say that federal law preempts Blackburn's state-law cause of action. Based on this conclusion, our previous opinion, and the Supreme Court of Alabama's answers to our certified questions, we REVERSE and REMAND for further proceedings.

Appendix B

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

No. 20-12258

MARK BLACKBURN,

Plaintiff-Appellant,

v.

SHIRE U.S., INC., SHIRE, LLC,

Defendants-Appellees.

SHIRE DEVELOPMENT, LLC, et al.,

Defendants.

Filed: Jan. 5, 2023

Before JILL PRYOR, LUCK, and BRASHER,
Circuit Judges.

ORDER

ON PETITION(S) FOR REHEARING AND PETITION(S) FOR REHEARING EN BANC

PER CURIAM:

The Petition for Rehearing En Banc is DENIED, no judge in regular active service on the Court having requested that the Court be polled on rehearing en

banc. (FRAP 35) The Petition for Panel Rehearing is also denied. (FRAP 40)

Appendix C

SUPREME COURT OF ALABAMA

No. 1210140

MARK BLACKBURN,

Plaintiff,

v.

SHIRE U.S., INC., SHIRE, LLC,

Defendants.

Filed: Sept. 30, 2022

OPINION

Pursuant to Rule 18, Ala. R. App. P., the United States Court of Appeals for the Eleventh Circuit has certified to this Court the following questions:

> "1. 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?
>
> "2. 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?"

Blackburn v. Shire US Inc., 18 F.4th 1310, 1322 (11th Cir. 2021) ("*Blackburn II*"). This Court accepted and now answers those questions.

I. Facts

Dr. Dino Ferrante, a gastroenterologist, prescribed LIALDA, which is manufactured by Shire U.S., Inc., and Shire, LLC (referred to collectively as "Shire"), to help patient Mark Blackburn with his Crohn's disease. "LIALDA is the brand name for Shire's mesalamine drug, which is an anti-inflammatory drug specifically aimed at the gut. LIALDA is not approved by the FDA to treat Crohn's, but it is approved to treat ulcerative colitis, Crohn's 'sister' disease." *Blackburn II*, 18 F.4th at 1314. Thus, Dr. Ferrante prescribed LIALDA for an "off-label" purpose, but one that is common. After taking LIALDA for between 12 to 16 months, Blackburn discovered that he had developed kidney disease, specifically advanced chronic interstitial nephritis, which had resulted in irreversible scarring and had diminished his kidney function to 20% of normal capacity. As a result, Blackburn is awaiting a kidney transplant.

In November 2013, when Blackburn began taking LIALDA, the "Warnings and Precautions" portion of its label included the following:

> "**5.1 Renal Impairment**
>
> "Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as LIALDA that contain mesalamine or are converted to mesalamine.

> "It is recommended that patients have an evaluation of renal function prior to initiation of LIALDA therapy and *periodically while on therapy*. Exercise caution when using LIALDA in patients with renal dysfunction or a history of renal disease."

(Bold typeface in original; emphasis added.) The recommendation to "have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy" was included in LIALDA's first label when it was approved for distribution in 2007, and it is that portion of the label which is the basis of Blackburn's failure-to-warn claim. See Shire's brief, p. 7.

In June 2016, Blackburn sued Shire in the United States District Court for the Northern District of Alabama, alleging strict liability for failure to warn under the Alabama Extended Manufacturer's Liability Doctrine ("the AEMLD"), breach of express warranty, and fraud. The breach-of-warranty and fraud claims were dismissed, and Shire sought summary judgment on the failure-to-warn claim.

> "Mr. Blackburn does not contend that Shire failed to warn of possible kidney injury when using LIALDA. Instead, Mr. Blackburn alleges that the recommended 'periodic' evaluation 'constitutes a defective and unsafe instruction for safe use of LIALDA.' [Quoting Blackburn's complaint.] He contends that the term 'periodic' as generally used in drug labels refers to either semi-annual or annual testing and that Shire's warning should have 'provide[d] for blood testing of renal function

at intervals necessary to reasonably protect patients from LIALDA's potential renal toxicity.' [Quoting Blackburn's complaint.]

"Mr. Blackburn contends that the language regarding testing for renal function in Shire's warning should resemble language used by other manufacturers of mesalamine-based drugs. PENTASA, like LIALDA, is a 5-aminosalicylic acid ('5-ASA') or mesalamine-based drug. In the United Kingdom, PENTASA is marketed with the warning that patients 'should have renal function monitored, with serum creatinine levels measured prior to treatment start, every 3 months for the first year, then [every 6 months] for the next 4 years and annually thereafter.' Similarly, OCTASA, another 5-ASA drug, is marketed in the United Kingdom with the following instruction:

> "'It is recommended that all patients have an evaluation of their renal function prior to initiation of Octasa therapy and repeatedly whilst on therapy. As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. Short monitoring intervals early after the start of Octasa therapy will discover rare acute renal reactions. In the absence of an acute renal reaction monitoring intervals can be extended to every 3

> months and then annually after 5 years.'
>
> "Mr. Blackburn asserts that an appropriate label for LIALDA, a mesalamine-based drug, should include instructions recommending 'evaluation of renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year.' [Quoting Blackburn's complaint.] Mr. Blackburn contends that Shire's failure to include this testing regimen in the LIALDA package warning in the fall of 2013 proximately caused his kidney injury."

Blackburn v. Shire U.S., Inc., No. 2:16-cv-00963-MHH, June 1, 2020 (N.D. Ala. 2020) ("*Blackburn I*") (not published in Federal Supplement) (citations to the record omitted).

> "[Dr. Agata] Przekwas[, a nephrologist,] and Dr. Jonathan Winston, a nephrology expert retained by Blackburn, concluded that Blackburn's injuries were preventable. Winston estimated that Blackburn's kidney disease was detectable at least six months before it was diagnosed, and possibly as early as August 2014. If Blackburn had stopped taking LIALDA at that time, Winston opined that his kidney function 'would be either normal or near normal.' And Winston attributed Blackburn's injury to the LIALDA label. Because of the amorphous 'periodic' instruction, Winston reasoned that a

> physician following the label's warning could fail to detect kidney disease before it 'worsen[ed] to a clinically significant level.'
>
> "Benjamin England, a regulatory expert retained by Blackburn, explained that Shire could have changed the label to include a stronger monitoring instruction. He concurred in Winston's assessment of the label's inadequacies and added that sufficient evidence, including … 'a growing body of medical literature,' supported a stronger monitoring instruction. England also identified reports of renal impairment that Shire received between the label's initial approval and Blackburn's injury. He concluded that sufficient evidence would have led to a label change, had Shire sought one."

Blackburn II, 18 F.4th at 1315.

Dr. Ferrante testified that, to him, testing renal function "periodically" meant "once a year," though he "acknowledged that 'periodically' can mean other time periods as well and that there is no specific definition of 'periodically' in the medical profession." *Blackburn I*. He also stated that if the LIALDA label had contained language similar to the labels for PENTASA and OCTASA, mentioned in the initial quote from *Blackburn I* above, he "'would have followed those protocols.'" *Id.*

The federal district court granted Shire's summary-judgment motion, holding that there was an "absence of admissible evidence of a causal link between Shire's instructions for renal evaluations when prescribing LIALDA and Mr. Blackburn's

injury." *Blackburn I*. Blackburn appealed. The Eleventh Circuit Court of Appeals disagreed with the federal district court's application of the facts on summary judgment. It concluded that Dr. Ferrante's testimony that he did not read the LIALDA label should not have been interpreted as meaning that the label's contents did not matter to him but, rather, that "the existing label's warning was so well known to the physician that he did not read it before each new prescription." *Blackburn II*, 18 F.4th at 1319. Furthermore, the Eleventh Circuit Court of Appeals rejected the federal district court's conclusion that Dr. Ferrante's testimony that he would have altered his testing regimen for Blackburn if the LIALDA label had been different was "unsubstantiated speculation" and "self-interested" because such a conclusion "goes to credibility, not the usefulness of the testimony at summary judgment." *Id.* at 1320.

Even though the Eleventh Circuit Court of Appeals rejected the federal district court's basis for entering a summary judgment in favor of Shire, it acknowledged that Shire had presented an alternative basis for summary judgment.

> "As an alternative basis to affirm the district court's summary judgment, Shire argues that the district court erred in recognizing Blackburn's theory of liability as a matter of Alabama law. There are two parts to this argument, as we see it. First, citing the learned intermediary doctrine, Shire contends that it satisfied its duty as a matter of law by warning of the risk of renal impairment and that, once a drug

> manufacturer warns of a risk, it is up to the prescribing doctor to assess and mitigate that risk. Second, Shire argues that Blackburn's theory of proximate cause is 'not in accord with Alabama law.' Specifically, Shire argues that a failure-to-warn plaintiff may establish that his injury was caused by a prescription drug only by showing that the physician would not have prescribed the drug if the warning had been adequate."

Id. at 1321. That alternative legal basis for summary judgment prompted the certified questions submitted to this Court.

II. Analysis

We initially note that both sides, in one legal forum or another, have contended that federal preemption warrants a ruling as a matter of law in its favor. The Eleventh Circuit Court of Appeals observed in its opinion:

> "Shire also argues that federal law would preempt a state law cause of action if it existed. The district court rejected this preemption defense. *See generally Wyeth v. Levine*, 555 U.S. 555, 581, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (2009). We will address it, if necessary, after we know the contours of state law. *See Blue Cross & Blue Shield of Ala., Inc. v. Nielsen*, 116 F.3d 1406, 1412 (11th Cir. 1997) (certifying a question because 'the state law issues must be decided before we can dispose of' the preemption question), *certified question answered*, 714 So. 2d 293 (Ala. 1998)."

Blackburn II, 18 F.4th at 1319 n.1. Before this Court, Blackburn argues that federal regulations mandate that prescription-drug labels have instructions regarding the required frequency of testing related to use of a prescription drug.

Regardless of whether either side is correct in its assertions, federal preemption is not an issue of Alabama law. To be answered by this Court, federal certified questions must be "questions or propositions of law *of this State* which are determinative of said cause and [for which] *there are no clear controlling precedents in the decisions of the Supreme Court of this State* ...." Rule 18(a), Ala. R. App. P. (emphasis added). Thus, unsurprisingly, certified questions concern Alabama law, not federal law. Federal preemption is an issue of federal law that the Eleventh Circuit Court of Appeals needs no assistance in evaluating. *See, e.g.*, *Glover v. Bausch & Lomb Inc.*, 6 F.4th 229, 241 n.9 (2d Cir. 2021) (noting that, "[b]ecause preemption is a question of federal law, ... we certify only the question of whether Connecticut law recognizes such a cause of action, and not whether that cause of action would be preempted under the [Food, Drug, and Cosmetic Act]"). Therefore, we decline to address the parties' arguments concerning federal preemption.

A. The First Certified Question

The first certified question probes the contours of a prescription-drug manufacturer's duty to warn under Alabama law. As the question indicates, in Alabama such a duty to warn is filtered through the "learned-intermediary doctrine," which essentially holds that the warning is directed toward the physician who prescribes a drug rather than the

patient who takes the drug. This Court first adopted the learned-intermediary doctrine in *Stone v. Smith, Kline & French Laboratories*, 447 So. 2d 1301 (Ala. 1984), in which the Court explained:

> "Plaintiffs-appellants misconceive the physician's role in prescribing ethical drugs, and the significance of a drug manufacturer's warning in undertaking that responsibility. A proper understanding of that role has been articulated by the United States Court of Appeals for the Fifth Circuit as follows:
>
> > "'We cannot quarrel with the general proposition that where *prescription* drugs are concerned, *the manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the drug's use*. This special standard for prescription drugs is an understandable exception to the Restatement's general rule that one who markets goods must warn for[e]seeable ultimate users of dangers inherent in his products. See Restatement (Second) of Torts, Section 388 (1965). 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. Pharmaceutical companies then, who must warn ultimate purchasers of dangers inherent in patent drugs sold over the counter, in selling prescription drugs are required to warn only the prescribing physician, who acts as a "learned intermediary" between manufacturer and consumer.'
>
> "*Reyes v. Wyeth Laboratories*, 498 F.2d [1264,] 1276 [(5th Cir. 1974)]."

447 So. 2d at 1304-05 (second emphasis added).

The Court last expounded on the learned-intermediary doctrine in *Wyeth, Inc. v. Weeks*, 159 So. 3d 649 (Ala. 2014), stating:

> "In *Stone v. Smith, Kline & French Laboratories*, 447 So. 2d 1301 (Ala. 1984), this Court adopted the learned-intermediary doctrine in a case addressing whether a manufacturer's duty to warn extends beyond the prescribing physician to the physician's patient who would ultimately use the drugs. *The principle behind the learned-intermediary doctrine is that prescribing physicians act as learned intermediaries between a manufacturer of a drug and the*

consumer/patient and that, therefore, the physician stands in the best position to evaluate a patient's needs and to assess the risks and benefits of a particular course of treatment for the patient. A consumer can obtain a prescription drug only through a physician or other qualified health-care provider. 21 U.S.C. § 353(b)(1). Physicians are trained to understand the highly technical warnings required by the FDA in drug labeling. 21 C.F.R. § 201.56. The learned-intermediary doctrine was established in *Marcus v. Specific Pharmaceuticals*, 191 Misc. 285, 77 N.Y.S.2d 508 (N.Y. Sup. Ct. 1948), as an absolute defense for 'failure to warn' cases. Mitesh Bansilal Shah, Commentary, *As a Matter of Fact or a Matter of Law: The Learned Intermediary Doctrine in Alabama*, 53 Ala. L. Rev. 1299, 1301 (2002). …

"The learned-intermediary doctrine recognizes the role of physician as a learned intermediary between a drug manufacturer and a patient. As the United States Court of Appeals for the Eleventh Circuit has explained:

> "'In cases involving complex products, such as those in which pharmaceutical companies are selling prescription drugs, the learned intermediary doctrine applies. Under the learned intermediary doctrine, a

> manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the use of its product. This standard is "an understandable exception to the Restatement's general rule that one who markets goods must warn foreseeable ultimate users of dangers inherent in his products." As such, we rely on the expertise of the physician intermediary to bridge the gap in special cases where the product and related warning are sufficiently complex so as not to be fully appreciated by the consumer.... "[U]nder the 'learned intermediary doctrine' the adequacy of [the defendant's] warning is measured by its effect on the physician, ... to whom it owed a duty to warn, and not by its effect on [the consumer]."'

"*Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313-14 (11th Cir. 2000) (citations omitted).

"A prescription-drug manufacturer fulfills its duty to warn the ultimate users of the risks of its product by providing adequate warnings to the learned intermediaries who prescribe the drug. Once that duty is fulfilled, the manufacturer has no further duty to warn the patient directly. However, if the warning to

> the learned intermediary is inadequate or misrepresents the risk, the manufacturer remains liable for the injuries sustained by the patient. *The patient must show that the manufacturer failed to warn the physician of a risk not otherwise known to the physician and that the failure to warn was the actual and proximate cause of the patient's injury. In short, the patient must show that, but for the false representation made in the warning, the prescribing physician would not have prescribed the medication to his patient."*

159 So. 3d at 672-74 (emphasis added).[1]

The parties bicker at length concerning the import of *Stone* and (especially) *Weeks* on the certified questions. Shire contends that *Weeks* definitively answers both certified questions in the negative and that there is no need to consider "expanding a prescription drug manufacturer's duty to warn under the learned intermediary doctrine." Shire's brief, p. 18. As already noted, both *Stone* and *Weeks* acknowledged that "'manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the use of its

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[1] The *Weeks* Court concluded that a prescription-drug designer could be held liable for alleged injuries caused by a generic version of the drug that the designer did not manufacture. As this Court noted in *Forest Laboratories, LLC v. Feheley*, 296 So. 3d 302, 316 (Ala. 2019), the Alabama Legislature enacted § 6-5-530, Ala. Code 1975, in the year following the *Weeks* decision, which "abrogates this Court's prior decision in *Weeks*. … [U]nder the plain language of § 6-5-530, a pharmaceutical manufacturer cannot be held liable for injury caused by a product it did not manufacture."

product.'" *Weeks*, 159 So. 2d at 673 (quoting *Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313 (11th Cir. 2000)); *Stone*, 447 So. 2d at 1304 (quoting *Reyes v. Wyeth Lab'ys*, 498 F.2d 1264, 1276 (5th Cir. 1974), for the same proposition). *Weeks* also stated that "[t]he patient must show that the manufacturer failed to warn the physician of a risk not otherwise known to the physician …." 159 So. 3d at 673. Shire interprets those statements as meaning that a prescription-dug manufacturer's duty to warn consists *solely* of listing a drug's known side effects.[2] Thus, Shire takes the position that *Weeks* forecloses any notion that the duty to warn could include instructions for safely monitoring a patient while taking a prescription drug.

Blackburn, on the other hand, contends that a prescription-drug manufacturer's duty to warn is twofold: the manufacturer must warn of a drug's known side effects and it must warn about safe use of the drug. Blackburn argues that the formulations of the duty to warn expressed in Stone and Weeks were geared more toward the side-effect aspect of that duty because both of those cases ultimately concerned whether side-effect warnings had been adequate.[3] In

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[2] Shire drove home its position in oral argument when it asserted that if a prescription-drug manufacturer produces two drugs that have the same known side effect, but the side effect occurs quickly in one of the drugs and occurs very slowly in other drug, the drug manufacturer's only responsibility for both drugs is to list the side effect.

[3] In his brief to this Court, Blackburn also argued that the statements in *Weeks* concerning the duty to warn were not "good law" because the central holding in *Weeks* has been abrogated. Blackburn's brief, p. 25; see note 1, supra. Blackburn

Stone, the plaintiff contended that the prescription drug Thorazine had caused her to develop cholestatic jaundice. The plaintiff conceded that her "physician was adequately warned of the adverse side effects, including cholestatic jaundice," but she contended that "the warnings issued [were] of no consequence, because prescribing physicians cannot accurately predict which of their patients will develop jaundice as a result of treatment with Thorazine." *Stone*, 447 So. 2d at 1304. This Court rejected the plaintiff's contention because, it held, it was the physician's responsibility to "'take into account the propensities of the drug as well as the susceptibilities of his patient'" and to weigh "'the benefits of any medication against its potential dangers.'" *Id.* at 1305 (quoting *Reyes*, 498 F.2d at 1276). In *Weeks*, the plaintiff contended that prescription-drug designers had "materially misinformed and misled [the plaintiff's physician] about the likelihood that the [prescription] drug [Reglan] would cause the movement disorder tardive dyskinesia and related movement disorders." 159 So. 3d at 655. Blackburn asserts that the context of the allegations in those cases must be borne in mind when considering the statements that a prescription-drug manufacturer must warn a prescribing physician of "any potential dangers that may result from the use of its product" and that a plaintiff must demonstrate that a drug manufacturer "failed to warn the physician of a risk not otherwise known to the physician." *Weeks*, 159 So. 3d at 673. In other words, Blackburn argues that the mere fact that "side-effects

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categorically abandoned that position in oral argument before this Court.

cases" such as *Stone* and *Weeks* state that the duty to warn includes warning about known dangers of a prescription drug does not mean that such a duty cannot include instructions for mitigating those side effects.

For several reasons, we agree with Blackburn. First, the *Weeks* decision was not primarily concerned with outlining all the contours of a prescription-drug manufacturer's duty to warn. The duty to warn was discussed simply because the drug-designer defendants had contended that they had no relationship with the plaintiff because the plaintiff had ingested a generic version of Reglan that they did not manufacture. This Court rejected that argument by observing that the learned-intermediary doctrine and the fact that "the FDA mandates that the warning on a generic-drug label be the same as the warning on the brand-name-drug label" rendered the plaintiff's lack of a relationship with the drug's designers irrelevant. *Weeks*, 159 So. 3d at 674. In other words, the duty to warn was only an issue in *Weeks* because, according to the Court, what mattered was the drug label's communication to the plaintiff's physician, and the labeling on the generic version of Reglan was controlled by the drug's designers. Because *Weeks* concerned retail-drug-designer liability for alleged harms caused by a generic version of a drug, the decision did not settle whether a prescription-drug manufacturer's duty to warn only includes listing known side effects of a drug.

In fact, after the *Weeks* Court made the statements we quoted above, the Court more generally described the learned-intermediary doctrine as

providing "that a prescription-drug manufacturer fulfills its duty to warn users of the risk associated with its product by providing *adequate warnings* to the learned intermediaries who prescribe the drug and that, once that duty is fulfilled, the manufacturer owes no further duty to the ultimate consumer." 159 So. 3d at 674 (emphasis added). Whether a warning "adequate[ly]" warns users of a drug's risks certainly involves listing a drug's known side effects, but it also may include instructions for mitigating those side effects. This is so because merely listing a prescription drug's side effects may not sufficiently alert a physician to the nature of the danger of the drug's side effects. More specific to this case, it is one thing to state that LIALDA can cause kidney damage; it is another thing if the potential for such damage is so likely that frequent monitoring of renal function, rather than "periodic" monitoring, is advisable. In other words, recommendations about monitoring represent one method of informing a physician about the degree of danger associated with a particular side effect. If a prescription-drug manufacturer knows the extent of a side effect's danger, then instructions about monitoring certainly could be part of warning about the drug's dangers. From that perspective, Blackburn is simply questioning whether LIALDA's instruction about "periodic" testing was sufficient to alert his physician as to the danger posed by LIALDA's side effect of kidney damage. Cf. *Stahl v. Novartis Pharms. Corp.*, 283 F.3d 254, 270 (5th Cir. 2002) (stating that "[t]here appears to be no compelling reason to exempt recommended medical monitoring schemes—which are, in essence, instructions for safe use of prescription drugs—from a drug manufacturer's duty to warn" and

observing that "many courts applying the law of other states have implicitly assumed that medical monitoring recommendations contained in package inserts are 'warnings' by evaluating such recommendations (or the absence of such recommendations) in determining whether a drug manufacturer has fulfilled its duty to warn").

That an adequate warning might have to include instructions for mitigating side effects becomes even more apparent through a closer examination of *Stone*. As Blackburn notes, in the course of adopting the learned-intermediary doctrine, the Stone Court also adopted Comment k to § 402A of the *Restatement (Second) of Torts* (Am. L. Inst. 1965) ("the *Restatement*"). See *Stone*, 447 So. 3d at 1303 (stating that "[t]he [federal] district court rightly recognized the applicability of Comment k to Section 402A of the Restatement (Second) of Torts (1965) … to the facts of this case"). In *Purvis v. PPG Industries, Inc.*, 502 So. 2d 714, 718 (Ala. 1987), this Court explained:

> "In *Stone v. Smith, Kline & French Laboratories*, 447 So. 2d 1301 (Ala. 1984), this Court, adopting comment k to Section 402A of the *Restatement (Second) of Torts*[] (1965)[, concluded that] an unavoidably unsafe product, when properly prepared and accompanied by proper directions and warnings, is not 'defective' or 'unreasonably dangerous' under Alabama's Extended Manufacturer's Liability Doctrine."

(Footnote omitted.) Comment k to § 402A of the *Restatement* provides:

> "k. *Unavoidably unsafe products*. 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. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and *accompanied by proper directions and warning*, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. ... The seller of such products, again *with the qualification that they are properly prepared and marketed, and proper warning is given*, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk."

(First and third emphasis added.) The adoption of Comment k in Stone provided a strong indication that a prescription-drug manufacturer's duty to warn is not

necessarily limited to listing a drug's known side effects but also may include directions for mitigating those side effects.[4]

The definition of a "product liability action" in § 6-5-501(2), Ala. Code 1975, provides further support for the fact that a failure-to-warn claim against a prescription-drug manufacturer may include a failure to provide adequate directions for using the drug. Section 6-5-501(2) provides:

> "(2) Product liability action. Any action brought by a natural person for personal injury, death, or property damage caused by the manufacture, construction, design, formula, preparation, assembly, installation, testing, *warnings, instructions, marketing, packaging, or labeling* of a manufactured product when such action is based upon (a) negligence, (b) innocent or negligent misrepresentation, (c) the manufacturer's liability doctrine, (d) the Alabama extended manufacturer's liability doctrine, as it exists or is hereafter construed or modified, (e) breach of any implied warranty, or (f) breach of any oral express warranty and no other. A product liability action does not include an action for contribution or indemnity."[5]

(Emphasis added.)

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[4] We note that Shire was conspicuously silent in its brief and at oral argument with respect to Blackburn's observations about Comment k to § 402A of the *Restatement*.

[5] Blackburn correctly notes that § 6-5-521(a), Ala. Code 1975, contains an identical definition of a "product liability action."

Shire discounts the foregoing legal definition as too generic to be of any use to our analysis of the issue at hand. But it is telling that "warnings" and "instructions" are listed together and that they are mentioned along with a product's "labeling." What this definition shows is that inadequate instructions on a label for a product are not outside the bounds of an AEMLD product-liability action. Shire has pointed us to nothing beyond its cramped readings of *Stone* and *Weeks* to demonstrate that Alabama law specially limits this aspect of the duty to warn for prescription-drug manufacturers in a way it does not for the manufacturer of any other product.

In place of an argument supported by Alabama law, Shire substitutes a policy argument: Shire insists that allowing instructions for mitigating warned-of risks to be part of a drug manufacturer's duty to warn intrudes upon a physician's practice of medicine. According to Shire, "once a physician is advised of the risks of a drug, he or she will use that information, together with her or his medical training and knowledge of a particular patient, to determine if the drug should be prescribed, and how the patient should be followed and monitored." Shire's brief, p. 15. Further, Shire argues that its view of "[a] prescription drug manufacturer's duty under the learned intermediary doctrine is consistent with the one-on-one relationship a patient has with his or her physician, as compared to the non-existent relationship between a patient and a prescription drug manufacturer." *Id.*, p.17.

Shire's contention is undermined by the fact that LIALDA's current label already includes instructions

for monitoring: "It is recommended that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy." If that instruction does not interfere with a physician's practice of medicine, it is difficult to see why Blackburn's desired instruction of monitoring a patient's renal function "on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year" represents the drastic intrusion upon the physician-patient relationship that Shire claims it to be. It cannot be because Blackburn's desired instruction is more specific. After all, as this Court has said, the goal of requiring a prescription-drug manufacturer to provide a warning is to enable a physician to be able to make an "informed" decision, i.e., "'an individualized medical judgment bottomed on a knowledge of both patient and palliative.'" *Weeks*, 159 So. 3d at 673 (quoting *Reyes*, 498 F.2d at 1276). Providing a physician more information presumably improves the physician's treatment of a patient. Indeed, a duty to warn that includes adequate instructions for mitigating warned-of risks does not interfere with the doctor-patient relationship any more than the presence of a drug label does in the first place. For example, in this case, LIALDA's label expressly states that it is approved for the treatment of ulcerative colitis, but that instruction obviously did not deter Dr. Ferrante from making his own medical judgment of prescribing it for Blackburn's Crohn's disease. Prescription drugs ordinarily include dosage recommendations for how often a patient should take a particular drug, but physicians freely modify those recommendations based on a patient's needs and

tolerance of the medication in question. The same would be true of an instruction for monitoring: even if LIALDA's label recommended testing a patient's renal function at certain specific intervals, rather than recommending "periodic" testing, a physician could deviate from the recommended course of monitoring based on his or her own medical judgment of what would be prudent for a particular patient.

The real issue is not whether instructions for monitoring would interfere with physician responsibility, but whether warnings about side effects of a prescription drug are sufficient in themselves to apprise physicians of a prescription drug's dangers. The ostensible answer would seem to be that it depends upon the drug in question. But nothing in Alabama's learned-intermediary doctrine prevents Blackburn from asserting a claim alleging that a failure to provide adequate monitoring instructions violates Shire's duty to warn. And that is the issue posed by the first certified question: Has Blackburn stated a viable cause of action under Alabama law with respect to Shire's duty to warn physicians about LIALDA? The answer is yes.

The parties have mentioned several facts in their briefs and at oral argument that are not within the purview of our assessment. For example, Shire's assertion that Dr. Ferrante failed to follow the LIALDA label as written and would not have followed Blackburn's desired warning has nothing to do with the aspect of a failure-to-warn claim we have been tasked with explicating. Likewise, whether there is a medical consensus about the frequency of monitoring that is necessary when taking a mesalamine drug is a

fact question that is not properly before us. In answering the first question presented, we are strictly concerned with the scope of a prescription-drug manufacturer's duty to warn physicians. Blackburn's claim does not exceed the boundaries of that duty. Accordingly, we answer the first certified question in the affirmative.

B. The Second Certified Question

Our answer to the second question flows naturally from our conclusion concerning the first question. Given that we have concluded that a failure-to-warn claim may include allegations of inadequate instructions about how to mitigate warned-of risks, it follows that a plaintiff may establish causation by showing that his or her physician would have adopted a different course of testing or mitigation, even though the physician would have prescribed the same drug. As Blackburn observes: "Instructions for safe use ... generally provide direction on how to minimize risk while using *this* product." Blackburn's reply brief, p. 31. Indeed, "mitigation" implies lessening risk *during use* of the product. It defies logic to require a plaintiff to demonstrate that his or her physician would not have prescribed a subject drug with respect to an allegation that the drug's warnings provide insufficient instruction for monitoring a patient while taking the drug.

Shire's arguments asserting otherwise rely almost entirely upon the statement from *Weeks* that "the patient must show that, but for the false representation made in the warning, the prescribing physician would not have prescribed the medication to his patient." 159 So. 3d at 673-74. But as we observed

in Part A of our analysis, the *Weeks* Court was not attempting to encapsulate the entirety of duty-to-warn law with respect to prescription-drug manufacturers; it was simply providing a summary in the context of a case alleging misinformation about the side effects of a drug. As Blackburn notes, several federal-court decisions applying Alabama law have intimated that a plaintiff may demonstrate causation by showing that a different warning from a prescription-drug manufacturer would have caused the plaintiff's physician to act differently, even if the physician still would have recommended the drug or procedure in question.

In *Barnhill v. Teva Pharmaceuticals, USA, Inc.*, 819 F. Supp. 2d 1254, 1261 (S.D. Ala. 2011), the United States District Court for the Southern District of Alabama explained:

> "*Theoretically, proof of proximate cause could take one of two forms*: (1) evidence that Dr. Jaalouk would not have prescribed cephalexin at all if the warning had been stronger or (2) *evidence that, though she still would have prescribed cephalexin, Dr. Jaalouk would have changed her behavior or treatment in some way that would have resulted in a different outcome for the Plaintiff*. As to the latter argument, the record is devoid of any evidence that the outcome would have been better or different … if the cephalexin had been prescribed or administered in a different manner.[6]
>
> "

> "[6] For example, there is no reason to believe that Plaintiff's SJS [Steven-Johnson syndrome] would have been diagnosed earlier or treated differently if Dr. Jaalouk had taken different precautions when she prescribed the drug, such as warning Plaintiff or her mother of the potential for SJS."

819 F. Supp. 2d at 1261 (emphasis added). In *Fields v. Eli Lilly & Co.*, 116 F. Supp. 3d 1295 (M.D. Ala. 2015), the United States District Court for the Middle District of Alabama discussed the Eleventh Circuit Court of Appeals' decision in *Toole v. McClintock*, 999 F.2d 1430 (11th Cir. 1993) ("*Toole*").

> "In *Toole*, the plaintiff developed scar tissue around her silicone breast implants and underwent a closed capsulotomy, a procedure where a surgeon manually compresses the affected breast to rupture the scar tissue. This procedure ruptured her breast implants, causing serious injuries. The plaintiff sued the manufacturer of her breast implants, alleging that it had failed to warn her doctor of the risk of ruptures during a closed capsulotomy. 999 F.2d at 1431. The jury returned a verdict in the plaintiff's favor, and the Eleventh Circuit affirmed the district court's denial of the manufacturer's motion for a directed verdict, rejecting the manufacturer's argument that there was 'no evidence that a different warning from [the manufacturer] would have caused [the plaintiff's physician] to behave differently.' *Id.* at 1433.

> "Applying Alabama's learned-intermediary doctrine, the Eleventh Circuit held that a reasonable jury could have found that the manufacturer's warning 'understated the risks of implant rupture from closed capsulotomies' and that the jury heard evidence that '*a different warning would have caused [the physician] to warn [the plaintiff] before her augmentation surgery*.' *Id.* (emphasis added). Hence, *the physician would have behaved differently had the manufacturer issued a stronger warning* because he testified that he would have warned the plaintiff of the risk of implant rupture prior to performing the augmentation surgery."

116 F. Supp. 3d at 1306-07 (second emphasis added). In *Cooper v. Bristol-Myers Squibb Co.*, Civil Action No. 07-885 (FLW), Jan. 7, 2013 (D. N.J. 2013) (not published in Federal Supplement), applying Alabama law and relying on both *Barnhill* and *Toole*, the federal district court in New Jersey stated:

> "Conversely, a plaintiff may demonstrate proximate cause by showing that the new warning would have changed the physician's calculation of the risks and benefits of the drug and caused the physician not to prescribe the drug. *See Brasher* [*v. Sandoz Pharms. Corp.*, No. CV-98-TMP-2648-S, Sept. 21, 2001 (N.D. Ala. 2001) (not published in Federal Supplement)]. Alternatively, *where the new warning would not have caused the physician to alter his prescribing habits, a*

> *plaintiff may demonstrate proximate cause by showing that the new warning would have at least 'changed [the physician's] ... treatment in some way that would have resulted in a different outcome for [the] Plaintiff.' Barnhill*, 819 F. Supp. 2d at 1261; see also *Toole*, 999 F.2d at 1433 (denying summary judgment on proximate cause grounds where physician testified that had he known 'in 1981 that there was a—even a slightly significant instance of rupture of the implants, then *I would have ... warned my patient*.') (emphasis added)."

(First emphasis added; footnote omitted.)

Shire ineffectively attempts to distinguish the foregoing authorities. Regarding *Barnhill*, Shire states that "*Barnhill* was referenced in *Weeks*, but the proximate cause theory was not mentioned and the express language of *Weeks* is contrary to the theory." Shire's brief, p. 58. But *Barnhill* was cited only in passing in the *Weeks* opinion's rendition of the facts that quoted from the federal district court's opinion posing the certified questions. See *Weeks*, 159 So. 3d at 654. The *Weeks* Court said nothing—positive or negative—about the *Barnhill* Court's understanding of the causation element of a prescription-drug duty-to-warn claim.

Shire argues that in *Fields* the court "relied on a misreading of *Toole*" and "completely ignor[ed] the differences between the practice of medicine and the role of pharmaceutical manufacturers." Shire's brief, p. 59. But that latter point amounts to disagreeing with the *Fields* court's conclusion, not distinguishing

it, and it is Shire that misreads *Toole*, not the *Fields* court. Shire contends that the *Toole* court adopted "the defendant's causation argument in that case based on patient choice" when it considered the fact that the plaintiff's doctor would have provided a different warning to the plaintiff about the procedure if he had known about the true danger of the implants rupturing. *Id.*, p. 58 (emphasis omitted). Shire argues that the *Toole* defendant's selection of a defense strategy "does not change the standard for proximate cause." *Id.*, p. 59. However, Shire confuses "patient choice" and what effect a warning may have on a physician. The *Toole* court explained that defendant Baxter Healthcare Corporation ("Baxter") made three arguments against the jury's conclusion that Baxter had provided an inadequate warning with respect to the risk of rupture for its implants.

> "Baxter contends that the district court erred in denying its motions for directed verdict and JNOV for three reasons. Baxter argues that its warning was clear that a closed capsulotomy could rupture the implant, that Ms. Toole admitted that, had the manufacturer's warnings been conveyed to *her*, she would not have consented to implant surgery, *and that there is no evidence that a different warning from Baxter would have caused Dr. McClintock to behave differently*. These arguments have insufficient merit."

Toole, 999 F.2d at 1433 (second emphasis added). The *Toole* court expressly *rejected* Baxter's "patient choice" argument because, "[u]nder the 'learned intermediary doctrine,' the adequacy of Baxter's warning is

measured by its effect on the *physician*, Dr. McClintock, to whom it owed a duty to warn, and not by its effect on Ms. Toole." *Id.* The *Toole* court then concluded that "[t]he jury heard evidence from which it could reasonably conclude that a different warning would have caused Dr. McClintock to warn Ms. Toole before her augmentation surgery." *Id.* Thus, the *Toole* court plainly concluded that causation based on the allegedly inadequate warning could be established by showing the difference in behavior an adequate warning would have produced upon Dr. McClintock, not just by showing whether Dr. McClintock would have recommended not doing the surgery at all.

Decisions applying the law of other jurisdictions also support this view. For example, *Bee v. Novartis Pharmaceuticals Corp.*, 18 F. Supp. 3d 268 (E.D. N.Y. 2014), applying New York law, clearly explained the view that "even where a physician admits to continued recommendation of a drug, despite knowing of its ... risk, changes to that doctor's prescription or treatment procedures will generate triable questions of fact on the question of causation," and *Bee* cited cases from several jurisdictions, including multi-district litigation against prescription-drug manufacturers, reaching the same conclusion. 18 F. Supp. 3d at 294-95. Other such cases include: *Knight v. Boehringer Ingelheim Pharms., Inc.*, 323 F. Supp. 3d 809, 831-33 (S.D. W. Va. 2018) (applying West Virginia law); *In re Xarelto (Rivaroxaban) Prod. Liab. Litig.*, MDL No. 2592, Apr. 17, 2017 (E.D. La. 2017) (unpublished order) (applying Louisiana law); and *Holley v. Gilead Scis., Inc.*, 379 F. Supp. 3d 809, 831-32 (N.D. Cal. 2019) (citing cases from several jurisdictions). See also *Schrecengost v. Coloplast Corp.*, 425 F. Supp. 3d 448,

463 (W.D. Pa. 2019) (involving a medical device and applying Pennsylvania law).

The plethora of authorities running in the same direction undercuts Shire's assertion that limiting causation to whether a physician would have prescribed a drug at all comports with drawing clear lines between a prescription-drug manufacturer's responsibility and a physician's practice of medicine with a patient.

> "The Court's holding in *Weeks* that prescription drug manufacturers should be held liable only for not disclosing risks of their drugs of which a physician is not aware and which would cause the physician to not prescribe the drug, reflects legal policy that manufacturers should not be liable for the outcome of physician/patient discussions and the decisions arising from those discussions. That legal policy judgment is consistent with the separateness of the physician/patient relationship underlying the learned intermediary doctrine the Court has cited. It is a policy that recognizes pharmaceutical manufacturers have no control over what is or what is not discussed between physicians and patients or the decisions resulting from those discussions, including patient choice decisions."

Shire's brief, pp. 52-53. That argument is a red herring. The issue at the heart of the second certified question is whether information provided by a prescription-drug manufacturer would have changed how a *physician* chose to monitor a patient and

whether such a change would have prevented the alleged harm suffered by the patient. More broadly, the learned-intermediary doctrine focuses on a prescription-drug manufacturer's communication to the physician, not to the patient, and the communication's effect on the physician's prescription and treatment of the patient with the subject drug. Obviously, if a physician changes a course of monitoring or treatment because of discussions the physician had with the patient, not because of information that should have been provided on the drug's label, then any causal link between the drug manufacturer's warnings and the patient's injuries is severed.

Allowing a plaintiff to demonstrate causation by presenting evidence indicating that the physician would have changed his or her course of treatment or monitoring of the plaintiff when a failure-to-warn claim concerns allegedly inadequate instructions for mitigating warned-of risks makes logical sense, and it is not foreclosed by Alabama precedent. Accordingly, we answer the second certified question in the affirmative.

III. Conclusion

For the foregoing reasons, we answer the questions certified to this Court in the affirmative.

QUESTIONS ANSWERED.

Parker, C.J., and Bolin, Wise, Bryan, Stewart, and Mitchell, JJ., concur.

Shaw, J., dissents.

Sellers, J., dissents, with opinion.

SELLERS, Justice (dissenting).

I respectfully dissent. In 1984, this Court adopted the learned-intermediary doctrine and held that prescription-drug manufacturers have a duty to warn prescribing physicians of the known risks of prescription drugs:

> "'[W]here prescription drugs are concerned, the manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the drug's use. This special standard for prescription drugs is an understandable exception to the Restatement's general rule that one who markets goods must warn foreseeable ultimate users of dangers inherent in his products. See Restatement (Second) of Torts, Section 388 (1965). 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. Pharmaceutical companies then, who must warn ultimate purchasers of dangers inherent in patent drugs sold over the counter, in selling prescription drugs are required to warn only the prescribing

> physician, who acts as a "learned intermediary" between manufacturer and consumer.'"

Stone v. Smith, Kline & French Lab'ys, 447 So. 2d 1301, 1304-05 (Ala. 1984) (quoting *Reyes v. Wyeth Lab'ys*, 498 F.2d 1264, 1276 (5th Cir. 1974)) (emphasis omitted).

"[T]he learned-intermediary doctrine addresses the question of liability in light of the relationships between the parties involved in the prescribing, distribution, and use of prescription drugs." *Nail v. Publix Super Mkts., Inc.*, 72 So. 3d 608, 614 (Ala. 2011). In the nearly 40 years since *Stone* was decided, this Court has interpreted the learned-intermediary doctrine as requiring a prescription-drug manufacturer to *warn* prescribing physicians of the known *risks* of drugs. *Stone*, supra; *Walls v. Alpharma USPD, Inc.*, 887 So. 2d 881, 884 (Ala. 2004); *Wyeth, Inc. v. Weeks*, 159 So. 3d 649, 673 (Ala. 2014). I would not expand that duty to mandate that prescription-drug manufacturers must also instruct physicians on how to specifically monitor or mitigate those risks.

Physicians, not drug manufacturers, are in the best position to evaluate patients to determine, based on a particular patient's unique medical history, personal features, and individual characteristics, whether to prescribe medication in the first place and how each patient should be monitored thereafter. *See Weeks*, 159 So. 3d at 673 ("[T]he physician stands in the best position to evaluate a patient's needs and to assess the risks and benefits of a particular course of treatment for the patient."), superseded by statute on other grounds, as recognized in *Forest Lab'ys, LLC v.*

Feheley, 296 So. 3d 302, 315 (Ala. 2019); *Walls*, 887 So. 2d at 886 ("'Neither [drug] manufacturer nor pharmacist has the medical education or knowledge of the medical history of the patient which would justify a judicial imposition of a duty to intrude into the physician-patient relationship.'" (quoting *McKee v. American Home Prods. Corp.*, 113 Wash. 2d 701, 711, 782 P.2d 1045, 1051 (1989))); *In re Chantix (Varenicline) Prod. Liab. Litig.*, 881 F. Supp. 2d 1333, 1342 (N.D. Ala. 2012) (indicating that a drug manufacturer did not have a duty to instruct prescribing physicians not to use a particular drug as a first line treatment for smoking addiction and noting that, "as other courts have recognized, it is the responsibility of the physician as a learned intermediary to assess the risks and benefits of a particular course of treatment"). As Shire U.S., Inc., and Shire, LLC (referred to collectively as "Shire"), state in their brief to this Court, "physicians routinely make decisions about following patients and deciding what monitoring will be done over a wide range of conditions and factors" and, "[i]n making those decisions, physicians factor in avoidance of unnecessary testing because of concerns about inconvenience and expense for patient[s]." Shire's brief at 22-23. Imposing a duty on a prescription-drug manufacturer to instruct physicians on how patients should be monitored while on prescription medication could very well interfere with the physician-patient relationship by forcing physicians to choose whether to follow the drug manufacturer's instructions or to instead rely on their own education and experience with each individual patient, with whom the drug manufacturer has had no contact. Evaluating the

efficacy of any drug regimen and its impact on a patient is best left to the physician, who is best able to fully interpret any risks and the suitability for continued treatment. Imposing the duty Mark Blackburn urges essentially forces prescription-drug manufacturers into the role of medical providers.

The Alabama statutory authority upon which Blackburn relies does not establish that prescription-drug manufacturers have a duty to instruct physicians on how to mitigate risks. Section 6-5-501(2), Ala. Code 1975, defines "product liability action" broadly for purposes of determining what actions are subject to the statute of limitations applicable to product-liability actions. Section 6-5-521(a), Ala. Code 1975, part of what has been commonly referred to as Alabama's "innocent-seller act," *see Lang v. Cabela's Wholesale, LLC*, [Ms. 1200851, June 24, 2022] ___ So. 3d ___, ___ n.1 (Ala. 2022), defines "product liability action" in the same manner as § 6-5-501(2), but for purposes of determining what actions are subject to the innocent-seller act. Although this definition of "product liability action" includes actions seeking damages for injuries caused by "instructions" accompanying a product, it in no way defines the scope of a prescription-drug manufacturer's duty. The word "instructions" is simply part of a long list of things related to a product that can form the basis of a product-liability action for purposes of the statutes at issue. Other things listed in the definition include, for example, "installation" and "construction," terms that hardly apply to prescription drugs. Product-liability actions commonly involve products like unavoidably dangerous tools, which necessarily must be accompanied by sufficient instructions for their use.

Obviously, the term "instructions" would apply to those types of actions. But nothing indicates that the legislature intended that each thing listed in the definition of "product liability action" applies to every type of product-liability action or that, by defining "product liability action," the legislature intended to delineate a prescription-drug manufacturer's duties.

The Alabama precedent upon which Blackburn relies, which involved actions based on allegedly insufficient instructions, are not prescription-drug cases. Rather, those cases involved medical *devices* or nonmedical products that necessarily required instructions for their use. Accordingly, the opinions in those cases do not establish that prescription-drug manufacturers must instruct physicians on how to mitigate risks in evaluating a patient after medication is prescribed.

As this Court reiterated in 2014, "'a [prescription-drug] manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the use of its product.'" *Weeks*, 159 So. 3d at 673 (quoting *Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313 (11th Cir. 2000)). Consistent with our precedent, I would hold that, once a prescription-drug manufacturer complies with its duty to warn of the known risks associated with a particular prescription drug, it is incumbent upon the learned intermediaries, not the drug manufacturer, to decide how to monitor patient compliance, the effectiveness of the drug, and the side effects incident to the drug's use that should be

mitigated. Thus, I would answer the first certified question in the negative.[6]

[6] Because Blackburn's only theory of liability is that Shire violated what I consider to be a nonexistent duty to provide different instructions to Blackburn's prescribing physician, the second certified question is, in my view, moot for purposes of this case. Thus, I would decline to answer it.

Appendix D

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

No. 20-12258

MARK BLACKBURN,

Plaintiff-Appellant,

v.

SHIRE U.S., INC., SHIRE, LLC,

Defendants-Appellees.

SHIRE DEVELOPMENT, LLC, et al.,

Defendants.

Filed: Nov. 29, 2021

Before JILL PRYOR, LUCK, and BRASHER,
Circuit Judges.

OPINION

BRASHER, Circuit Judge:

Under Alabama law, the manufacturer of an unreasonably dangerous product has a duty to warn users of the risks presented by the product. When the unreasonably dangerous product is a drug that requires a prescription, a drug manufacturer's duty to

warn is usually discharged by warning the prescribing physician of the product's risks.

Mark Blackburn was diagnosed with advanced stage kidney disease after taking LIALDA, a drug manufactured by Shire Pharmaceuticals. Blackburn does not contend that Shire failed to warn of the risk of kidney disease; he and his doctor knew that the drug might impair his kidney function. Instead, Blackburn contends that Shire should have more explicitly warned his doctor about how regularly to monitor his kidney function after prescribing LIALDA. He contends that, if LIALDA's warning label had been better, his physician would have monitored him differently after prescribing LIALDA, discovered the effect on his kidneys sooner, and prevented his injury.

In our view, Blackburn's theory of liability raises two unsettled questions of Alabama law. First, may a pharmaceutical company's duty to warn include a duty to provide instructions about how to mitigate warned-of risks? Second, may a plaintiff establish that an improper warning 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?

Because of how we resolve the federal issues in this appeal, these state-law questions are dispositive. For our part, we believe these questions are important enough—and the resolution uncertain enough—for us to certify them to the Supreme Court of Alabama.

I. BACKGROUND

Blackburn is a professional golf instructor. His training facility is located at a golf club in

Birmingham, Alabama, but he frequently travels throughout the world to counsel some of the world's best players and represent one of the game's premium brands. Blackburn suffers from Crohn's disease.

Prior to moving to Birmingham, he lived and worked at a golf course in Guntersville, Alabama. Dr. Craig Young was one of Blackburn's clients and his *de facto* primary care physician. Young ordered routine bloodwork for Blackburn, and his "labs looked good." About eighteen months later, Blackburn reported persistent gastrointestinal issues, and Young referred him to Dr. Dino Ferrante, a gastroenterologist in Huntsville, Alabama. Ferrante documented Blackburn's primary complaint as urgent diarrhea up to four times daily. Something Young said during his referral led Ferrante to conclude that he did not need to order initial bloodwork before treating Blackburn. After several tests and procedures, Ferrante diagnosed Blackburn with Crohn's disease.

Ferrante prescribed LIALDA, and Blackburn began taking the medication on November 6, 2013. LIALDA is the brand name for Shire's mesalamine drug, which is an anti-inflammatory drug specifically aimed at the gut. LIALDA is not approved by the FDA to treat Crohn's, but it is approved to treat ulcerative colitis, Crohn's "sister" disease. The drug is taken orally in pill form unlike other, more invasive Crohn's treatments, and Ferrante considered it the best option for Blackburn due to his travel schedule.

Mesalamine drugs like LIALDA pose a risk of kidney disease. The LIALDA label warns that "[r]enal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely,

renal failure, has been reported in patients given products such as LIALDA that contain mesalamine or are converted to mesalamine." Kidney disease is identified by a digression in kidney function over time. LIALDA can cause inflammatory cells to deposit in the kidneys, scarring organ tissue and diminishing kidney function. If a patient experiences this side effect, continuing to take the drug can lead to irreversible damage. To identify potential disease—and thereby prevent severe impairment—the label recommends "that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy." Renal function is evaluated by measuring the amount of creatinine in a patient's blood. Using the creatinine level, a physician can estimate glomerular filtration rate, which is a marker of how well a patient's kidneys are functioning.

Ferrante set a follow-up appointment for two months after he prescribed LIALDA, but either he or Blackburn canceled it. Even if Blackburn had kept the appointment, it is unlikely Ferrante would have ordered blood work to evaluate kidney function. As a matter of practice, Ferrante periodically tests renal function after "about a year" of treatment. By the time Blackburn had been taking LIALDA for a year, he had moved to Birmingham and requested a referral to a different doctor. Ferrante provided the referral, but Blackburn never followed up. Ferrante's office continued to fill Blackburn's prescriptions for over a year without examining him. Consequently, Blackburn's renal function went unmonitored during that time.

In all, Blackburn took LIALDA for somewhere between 12 and 16 months. He stopped filling the prescriptions in January 2015. Soon after that, Blackburn took himself off the drug because he felt that it wasn't working. He found that changing his diet partially relieved his Crohn's symptoms.

Soon after he stopped taking LIALDA, Blackburn discovered that he was suffering from advanced stage kidney disease. In April 2015, Blackburn underwent a blood test that revealed an excessive amount of creatinine, resulting in a low estimated glomerular filtration rate. His primary care physician referred him to Dr. Agata Przekwas, a nephrologist. Przekwas diagnosed Blackburn with advanced chronic interstitial nephritis, a type of kidney disease that manifests as irreversible scarring and diminished kidney function. The severity of kidney disease is expressed in six stages, with stage six requiring a patient to undergo dialysis. Blackburn's kidney disease was initially diagnosed as stage four, reflecting the fact that his kidneys were functioning at approximately 20 percent their normal capacity. Blackburn is currently awaiting a kidney transplant.

Przekwas and Dr. Jonathan Winston, a nephrology expert retained by Blackburn, concluded that Blackburn's injuries were preventable. Winston estimated that Blackburn's kidney disease was detectable at least six months before it was diagnosed, and possibly as early as August 2014. If Blackburn had stopped taking LIALDA at that time, Winston opined that his kidney function "would be either normal or near normal." And Winston attributed Blackburn's injury to the LIALDA label. Because of

the amorphous "periodic" instruction, Winston reasoned that a physician following the label's warning could fail to detect kidney disease before it "worsen[ed] to a clinically significant level."

Benjamin England, a regulatory expert retained by Blackburn, explained that Shire could have changed the label to include a stronger monitoring instruction. He concurred in Winston's assessment of the label's inadequacies and added that sufficient evidence, including a "a growing body of medical literature," supported a stronger monitoring instruction. England also identified reports of renal impairment that Shire received between the label's initial approval and Blackburn's injury. He concluded that sufficient evidence would have led to a label change, had Shire sought one.

Blackburn sued Shire in June 2016. Shire initially moved to dismiss for lack of personal jurisdiction and judgment on the pleadings. Blackburn sought leave to amend his complaint, and the district court ordered Shire to show cause why leave should not be granted. Shire responded that the amendments would be futile, but the district court granted Blackburn's motion anyway.

Blackburn originally asserted four claims under Alabama law: strict liability for failure to warn under the Alabama Extended Manufacturers Liability Doctrine, breach of express warranty, and two fraud claims. On Shire's second motion to dismiss, the district court dismissed with prejudice all but the failure-to-warn claim. Blackburn twice moved the district court to revive the dismissed counts. First, Blackburn moved the district court to alter its

dismissal to reflect that the counts were dismissed without prejudice, effectively granting him a second opportunity to amend his complaint. The district court denied the motion, concluding that Blackburn had forgone "ample opportunit[ies] to state claims on which relief could be granted." Instead of moving to amend his complaint while Shire's motion to dismiss was pending, Blackburn had "sat idly by" and waited for the district court to tell him whether his allegations were sufficient. Blackburn then moved for reconsideration, but the district court denied that motion as well. It concluded that the amendments would be futile because the LIALDA label did not create an express warranty for safeness that would support Blackburn's breach of express warranty or fraud-based claims.

Blackburn's remaining failure-to-warn claim alleged that the LIALDA label contained an inadequate warning regarding its potential renal toxicity. Specifically, Blackburn argued that if the label had provided more detailed instructions for safe use, his kidney disease would have been detected earlier. According to Blackburn, the label should have instructed prescribers to "evaluat[e] ... renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year." We refer generally to the label's language as the "periodic" renal function instruction to differentiate it from Blackburn's suggested "monthly" instruction.

Eventually, Shire moved for summary judgment. The district court approved of Blackburn's theory of

liability but held that it was not factually supported. Specifically, the district court granted judgment in favor of Shire because it concluded that the label's alleged inadequacies did not actually or proximately cause Blackburn's injuries. The district court concluded that it was undisputed that Ferrante did not rely on or even "look at the LIALDA label before he prescribed the drug." And Blackburn failed to demonstrate that Ferrante would have read and heeded an alternative instruction. Although Ferrante testified that he would have followed a more explicit instruction, the district court dismissed this testimony as "unsubstantiated speculation" and a "self-interested statement." Thus, Blackburn's claim failed on the facts, and the district court granted summary judgment to Shire.

II. STANDARDS OF REVIEW

We review both the denial of a motion for leave to amend a pleading and a motion for reconsideration for abuse of discretion. *Diaz v. Jaguar Rest. Grp., LLC*, 627 F.3d 1212, 1214 (11th Cir. 2010); *Corwin v. Walt Disney Co.*, 475 F.3d 1239, 1254 (11th Cir. 2007).

A district court's grant of summary judgment is reviewed *de novo*, with all facts and reasonable inferences therefrom viewed in the light most favorable to the nonmoving party. *Carmical v. Bell Helicopter Textron, Inc.*, 117 F.3d 490, 494 (11th Cir. 1997). Summary judgment is warranted only when there is no genuine issue as to any material fact, and the moving party is entitled to judgment as a matter of law. *T.W. ex rel. Wilson v. Sch. Bd. of Seminole Cnty.*, 610 F.3d 588, 597-98 (11th Cir. 2010); Fed. R. Civ. P. 56(a). We may affirm the district court on any

basis supported by the record. *Miller v. Harget*, 458 F.3d 1251, 1256 (11th Cir. 2006).

III. DISCUSSION

We divide our discussion into two main parts. First, we address whether the district court abused its discretion in denying Blackburn further opportunity to amend his complaint. Second, we address whether the district erred in granting summary judgment in favor of Shire.

A. The District Court Did Not Abuse its Discretion in Denying Blackburn Further Opportunities to Amend.

After Blackburn amended his complaint, the district court dismissed his warranty and fraud claims with prejudice. Blackburn moved the court to alter or amend its order to state that the dismissal was without prejudice and to allow him his "one chance" to amend. The court denied that motion, so Blackburn filed a motion for reconsideration, which the court again denied. Blackburn argues that the district court should have allowed him an opportunity to amend his complaint after it dismissed his warranty and fraud claims. Shire contends that Blackburn was not entitled to an additional opportunity to amend, and we agree.

A plaintiff has the right to amend his complaint within 21 days of serving it or 21 days after certain responsive pleadings and motions. Fed. R. Civ. P. 15(a)(1). In all other cases, the plaintiff requires leave of court or consent of the opposing party. Ordinarily, a court should "freely give" leave to amend a pleading "when justice so requires." Fed. R. Civ. P. 15(a)(2). Whether justice so requires is within the discretion of

the district court to determine. *See Burger King Corp. v. Weaver*, 169 F.3d 1310, 1319 (11th Cir. 1999).

As an initial matter, we reject Blackburn's argument that his complaint was first amended as a matter of right, such that his second request for leave to amend was his first such request. Before he filed his first amended complaint, Blackburn expressly sought leave to amend under Rule 15(a)(2)'s "freely given" standard, and he acknowledged that Shire's motion for judgment on the pleadings "cut off [his] ability to amend ... as a matter of right." *See* Fed. R. Civ. P. 15(a)(1). The district court then granted Blackburn leave to amend after considering Shire's opposing arguments. Thus, the district court afforded Blackburn an opportunity to amend his complaint that he was not entitled to as of right.

Nor can we say that the district court abused its discretion in denying the second motion to amend. When deciding whether to grant leave to amend, a court considers five factors: (1) undue delay, (2) bad faith or dilatory motive, (3) repeated failure to cure deficiencies by amendment, (4) undue prejudice to the opposing party by virtue of allowance of the amendment, and (5) futility. *Foman v. Davis*, 371 U.S. 178, 182 (1962); *Burger King Corp.*, 169 F.3d at 1319. Here, the district court based its decision to deny the motion on the undue delay and futility factors. The district court noted that Blackburn had "ample opportunity" and "sat idly by" as he awaited determination of Shire's second motion to dismiss. By the time the district court considered Blackburn's second request to amend, the parties and the court had spent significant time preparing and reviewing the

initial complaint, Shire's motion for judgment on the pleadings, Blackburn's response to that motion, Blackburn's first motion to amend, Shire's memorandum in response, and Blackburn's first amended complaint. The parties then again briefed the sufficiency of Blackburn's allegations, and the district court held that they were insufficient.

We find no abuse in the district court's conclusion that permitting such a late amendment "would be contrary to promoting judicial efficiency." A district court is not required to grant a counseled plaintiff leave to amend his complaint *sua sponte* before ruling on a dispositive motion. *Wagner v. Daewoo Heavy Indus. Am. Corp.*, 314 F.3d 541, 542 (11th Cir. 2002) (en banc). Accordingly, a plaintiff may not "sit idly by as he await[s] the district court's determination with respect to a Rule 12(b)(6) motion to dismiss." *Id.* at 543.

Relying on our decision in *Bryant v. Dupree*, 252 F.3d 1161, 1163 (11th Cir. 2001), Blackburn argues that, after the district court dismissed his first amended complaint, he was still entitled to one more chance to amend. But *Bryant* is distinguishable. The plaintiffs in *Bryant* amended their complaint once as a matter of course; then, in response to the defendant's motion to dismiss, the plaintiffs sought leave to amend a second time—while the motion to dismiss was still pending. *Id.* at 1163-64. Here, Blackburn did not first amend as a matter of course. And Blackburn did not seek leave to amend (a second time) until *after* the district court granted Shire's second dispositive motion. Blackburn's reliance on *Bryant* is therefore misplaced.

B. Summary Judgment on Failure to Warn

We now turn to the main issue—the district court's summary judgment on Blackburn's failure-to-warn claim. A prescription drug manufacturer has a duty to provide a warning that adequately apprises of the product's risks. *Stone v. Smith, Kline & French Lab'ys*, 447 So.2d 1301, 1304 (Ala. 1984). Because a prescription drug can be obtained only through an intermediary, such as a doctor, Alabama law assesses the adequacy of the warning by asking whether the warning label adequately warned that intermediary. *Wyeth, Inc. v. Weeks*, 159 So.3d 649, 673 (Ala. 2014), *superseded by statute on other grounds*, Ala. Code § 6-5-530, *as recognized in Forest Lab'ys, LLC v. Feheley*, 296 So.3d 302 (Ala. 2019). To succeed on a failure-to-adequately-warn claim, a plaintiff must show that the label's inadequacies actually and proximately caused his injury. *Gurley v. Am. Honda Motor Co.*, 505 So.2d 358, 361 (Ala. 1987). That is, the plaintiff must show that curing the label's inadequacies would have altered the prescribing physician's conduct in a way that would have prevented the plaintiff's injury. *See Weeks*, 159 So.3d at 673; *E.R. Squibb & Sons, Inc. v. Cox*, 477 So.2d 963, 970 (Ala. 1985).

Blackburn's theory of liability is that Shire provided his doctor inadequate instructions to mitigate the risk of impaired kidney function. Blackburn argues that the district court erred in concluding that, as a matter of undisputed fact, his doctor would have pursued the same course of treatment no matter the warning. For its part, Shire argues that Alabama tort law does not recognize a

cause of action based on a pharmaceutical company's failure to give mitigation instructions.

We agree with Blackburn that the district court erred in the way it viewed the record. We certify the question of whether Alabama law recognized this cause of action to the Supreme Court of Alabama.[1]

1. The district court overlooked disputes of material fact.

The district court considered three undisputed facts fatal to Blackburn's failure-to-warn claim: first, Ferrante did not read the LIALDA label before prescribing the drug to Blackburn; second, Ferrante never tested Blackburn's renal function; and third, Blackburn did not attend the follow-up appointment. From these three facts, the district concluded that the label's alleged inadequacies did not cause Blackburn's injuries as a matter of law. Blackburn argues that, despite these facts, genuine issues of material fact exist concerning causation because Ferrante testified that he would have read the label and treated Blackburn differently if the label carried a different warning. We agree with Blackburn.

As to the first issue, we believe the district court misunderstood Ferrante's testimony about reading

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[1] Shire also argues that federal law would preempt a state law cause of action if it existed. The district court rejected this preemption defense. *See generally Wyeth v. Levine*, 555 U.S. 555, 581 (2009). We will address it, if necessary, after we know the contours of state law. *See Blue Cross & Blue Shield of Ala., Inc. v. Nielsen*, 116 F.3d 1406, 1412 (11th Cir. 1997) (certifying a question because "the state law issues must be decided before we can dispose of" the preemption question), *certified question answered*, 714 So.2d 293 (Ala. 1998).

the label. Although Ferrante testified that he did not actually look at the LIALDA label before prescribing it to Blackburn, he also testified that he had prescribed the medication before, he was familiar with its existing label, and he knew that renal function should be monitored periodically. He explained that he complied with his interpretation of the label's instructions. And he said he would have followed a different label. In other words, this is not a case where the label's warning did not matter to the physician. It is instead a case where the existing label's warning was so well known to the physician that he did not read it before each new prescription.

The district court dismissed Ferrante's testimony about whether he would have read and incorporated a different label into his practices as "unsubstantiated speculation" and "self-interested" testimony. We disagree. Shire argues that Blackburn cannot create a genuine issue of material fact by speculating about whether he and Ferrante would have complied with a monthly monitoring instruction. We agree that a party may not avoid summary judgment by offering only his own speculation about a material fact. *See, e.g.*, *Cordoba v. Dillard's, Inc.*, 419 F.3d 1169, 1181 (11th Cir. 2005). But that is not what Blackburn has done.

As an initial matter, Ferrante's testimony is no more self-serving than any other kind of evidence that must be considered at summary judgment. We have held that "a litigant's self-serving statements based on personal knowledge or observation can defeat summary judgment." *United States v. Stein*, 881 F.3d 853, 857 (11th Cir. 2018); see also Fed. R. Civ. P. 56. Here, of course, Blackburn is relying on Ferrante's

testimony, not his own. It may be, as Shire argues, that Ferrante has some self interest in minimizing his role in causing Blackburn's adverse side effects. But this argument goes to credibility, not the usefulness of the testimony at summary judgment. *See Stein*, 881 F.3d at 857.

Ferrante's testimony is also not speculative, at least as we have used that term in addressing the usefulness of summary judgment evidence. The question under Blackburn's causation theory is whether a different label would have led to a different outcome for Blackburn, which turns on the factual question of what Ferrante would have done if the label had been different. As Blackburn's treating physician, Ferrante may testify on that issue. *See United States v. Henderson*, 409 F.3d 1293, 1300 (11th Cir. 2005) (citing Fed. R. Evid. 701); *see also* Fed. R. Evid. 704. And his testimony here is no more speculative than testimony we have considered when answering whether a change in label would have affected a doctor's treatment in other cases. *Toole v. McClintock*, 999 F.2d 1430, 1433 n.6 (11th Cir. 1993) (holding that a doctor's similar testimony supported sending a failure-to-warn claim to the jury).

The district court reasoned that Ferrante's "conduct" contradicted his testimony, but we fail to see how it reached that conclusion if it viewed the facts in Blackburn's favor, as it was required to do. Although Ferrante did not initially or periodically test Blackburn's renal function, he explained why: first, he relied on Young's indication that Blackburn's blood work "checked out" prior to the referral; and second, Blackburn requested a referral to a new doctor before

Ferrante would have ordered periodic bloodwork. Given his explanation for why he did not test Blackburn, a reasonable jury could find that Ferrante would have followed a different warning label.

Finally, the district court made an improper inference concerning the missed follow-up appointment. Blackburn's failure to attend the appointment would "sever[] the causal chain," as the district court concluded, only if a doctor would have tested his renal function at the appointment. But the record does not indicate that any doctor would have. Ferrante testified that the appointment was primarily to address any side-effects of the medication, that he did not typically assess renal function until much later, and that either he or Blackburn canceled the appointment. The district court was also persuaded that Blackburn would not have attended an appointment for a blood test, even if Ferrante ordered one. However, drawing inferences in Blackburn's favor, his failure to attend the follow-up appointment to assess medication side-effects was based on matters completely unrelated to whether he would have attended a testing appointment, such as not noticing any side effects from the medication. There is no other evidence that Blackburn would not have submitted to more frequent testing if his doctor had recommended it based on a different warning label.

Considering Ferrante's testimony, and drawing all inferences in Blackburn's favor, a reasonable jury could find that Ferrante would have read and heeded a different LIALDA label that warned of a need for more frequent testing. These genuine disputes of

material fact preclude us from affirming based on the district court's reasoning.

2. We certify two state law questions to the Supreme Court of Alabama.

As an alternative basis to affirm the district court's summary judgment, Shire argues that the district court erred in recognizing Blackburn's theory of liability as a matter of Alabama law. There are two parts to this argument, as we see it. First, citing the learned intermediary doctrine, Shire contends that it satisfied its duty as a matter of law by warning of the risk of renal impairment and that, once a drug manufacturer warns of a risk, it is up to the prescribing doctor to assess and mitigate that risk. Second, Shire argues that Blackburn's theory of proximate cause is "not in accord with Alabama law." Specifically, Shire argues that a failure-to-warn plaintiff may establish that his injury was caused by a prescription drug only by showing that the physician would not have prescribed the drug if the warning had been adequate. Shire's arguments present the following state-law questions:

> 1. 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?
>
> 2. 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?

We believe these questions are dispositive, but we confront a dearth of clear authority to resolve them.

We have not expressly addressed Shire's first argument. Some federal district courts have arguably accepted the argument. *See In re Chantix (Varenicline) Prods. Liab. Litig.*, 881 F. Supp. 2d 1333, 1342 n.12 (N.D. Ala. 2012) (dismissing the claim that a drug's label should have included prescribing instructions where the label "clearly set[] forth" the experienced side effect); *Dye v. Covidien LP*, 470 F. Supp. 3d 1329, 1341 (S.D. Fla. 2020) (holding that a drug manufacturer "need only warn of complications stemming from the use of the Product—not the subsequent measures medical professionals may employ to treat those complications"). On the other hand, the Fifth Circuit has concluded (applying Louisiana law) that "recommended medical monitoring schemes ... are, in essence, instructions for safe use of prescription drugs" that must be included to satisfy a manufacturer's duty to warn. *Stahl v. Novartis Pharms. Corp.*, 283 F.3d 254, 269-70 (5th Cir. 2002) (citing Restatement (Third) of Torts: Products Liability § 6(b) (1997) (noting that a prescription drug or medical device is defective if it "is not reasonably safe due to inadequate instructions or warnings" (emphasis omitted))); *see also PLIVA, Inc. v. Mensing*, 564 U.S. 611 (2011) ("a manufacturer's duty to warn includes a duty to provide adequate instructions for safe use of a product"). No decision of the Supreme Court of Alabama directly adopts either position. Although the court has at times used the terms "instructions" and "warnings" interchangeably, *Yarbrough v. Sears, Roebuck & Co.*, 628 So.2d 478, 483 (Ala. 1993), it has also said that a drug 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," *Weeks*, 159 So.3d at 673 (quoting *Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313-14 (11th Cir. 2000)).

As to Shire's second argument, the district court reasoned that "proof of proximate cause could also 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." We have arguably approved of this theory under Alabama law. *See Toole*, 999 F.2d at 1433. And several district court decisions also endorse this position. *See Barnhill v. Teva Pharms. USA, Inc.*, 819 F. Supp. 2d 1254, 1261 (S.D. Ala. 2011); *Fields v. Eli Lilly & Co.*, 116 F. Supp. 3d 1295, 1306 (M.D. Ala. 2015). But Shire argues with some force that this theory is in tension with the Supreme Court of Alabama's latest statements on causation in the pharmaceutical failure-to-warn context. *See Weeks*, 159 So.3d at 673-74 ("In short, the patient must show that, but for the false representation made in the warning, the prescribing physician would not have prescribed the medication to his patient.").

Thankfully, the Supreme Court of Alabama permits federal courts to certify questions when faced with "determinative" issues of state law upon which "there are no clear controlling precedents in the decisions of the Supreme Court [of Alabama]." Ala. R. App. P. 18(a). The "most important" factors in deciding to certify are "the closeness of the question and the existence of sufficient sources of state law ... to allow a

principled rather than conjectural conclusion." *Florida ex rel. Shevin v. Exxon Corp.*, 526 F.2d 266, 274-75 (5th Cir. 1976). Thus, certification is generally appropriate where we face "substantial doubt on a dispositive state law issue." *WM Mobile Bay Env't Ctr., Inc. v. City of Mobile Solid Waste Auth.*, 972 F.3d 1240, 1251 (11th Cir. 2020). Unsurprisingly, we have sought guidance from the Supreme Court of Alabama on similar issues of tort liability before. *See Farsian v. Pfizer, Inc.*, 52 F.3d 932, 934 (11th Cir. 1995), *certified question answered*, 682 So.2d 405 (Ala. 1996); *Campbell v. Cutler Hammer, Inc.*, 996 F.2d 1164, 1166 (11th Cir. 1993), *certified question answered*, 646 So.2d 573 (Ala. 1994). We believe it is the best course to seek the Supreme Court of Alabama's guidance again.

IV. CONCLUSION

Before we can decide whether to affirm or reverse the district court, we must determine whether Blackburn's theory of liability is consistent with Alabama law. We therefore certify to the Supreme Court of Alabama the following questions:

> 1. 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?
>
> 2. 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?

We defer our decision in this case until the Supreme Court of Alabama has considered our certified questions. We note that our phrasing of the certified questions is not intended "to restrict the Supreme Court's consideration of the problems involved and the issues as the Supreme Court perceives them to be in its analysis of the record certified in this case." *Martinez v. Rodriquez*, 394 F.2d 156, 159 n.6 (5th Cir. 1968). To that end, "if we have overlooked or mischaracterized any state law issues or inartfully stated [the] questions we have posed, we hope the Alabama Supreme Court will feel free to make the necessary corrections." *Spain v. Brown & Williamson Tobacco Corp.*, 230 F.3d 1300, 1312 (11th Cir. 2000). The entire record of this case, including the parties' briefs, is transmitted to the Supreme Court of Alabama.

QUESTIONS CERTIFIED.

Appendix E

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA

No. 2:16-CV-00963

MARK BLACKBURN,

Plaintiff,

v.

SHIRE U.S., INC., et al.,

Defendants.

Filed: June 1, 2020

MEMORANDUM OPINION[1]

In this prescription drug products liability case, plaintiff Mark Blackburn contends that defendants Shire U.S., Inc. and Shire, LLC, the makers of the prescription drug LIALDA, breached their obligation to provide adequate instructions for the safe use of the drug, and the breach proximately caused his chronic, irreversible kidney injury. According to Mr.

[1] The Court is issuing this opinion during a declared national emergency concerning COVID-19. To enable parties to pursue their rights during this emergency, the Court is continuing its work. For information about the timing of appeals, please review the information provided in the conclusion of this opinion. The Court is including this procedural information in each opinion that it issues during the national emergency.

Blackburn, if Shire had included in its written warning information that instructed prescribing physicians to perform renal assessments at specific intervals, his prescribing physician would have detected his kidney injury and altered the treatment he prescribed for Mr. Blackburn's Crohn's disease. The Shire defendants have asked the Court to enter judgment in their favor. (Doc. 194). For the reasons stated below, the Court will grant the defendants' motion for summary judgment.

STANDARD OF REVIEW

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." FED. R. CIV. P. 56(a). To demonstrate that there is a genuine dispute as to a material fact that precludes summary judgment, a party opposing a motion for summary judgment must cite "to particular parts of materials in the record, including depositions, documents, electronically stored information, affidavits or declarations, stipulations (including those made for purposes of the motion only), admissions, interrogatory answers, or other materials." Fed. R. Civ. P. 56(c)(1)(A). "The court need consider only the cited materials, but it may consider other materials in the record." Fed. R. Civ. P. 56(c)(3).

FACTS

Mr. Blackburn is an accomplished golf instructor. He coaches amateur and professional players on the PGA tour. He also speaks at conferences for Titleist, a company that produces golf apparel and equipment. Mr. Blackburn must travel nationally and

internationally for his work. Mr. Blackburn suffers from Crohn's disease, and the disease sometimes interferes with his work.

In November of 2013, Mr. Blackburn began taking LIALDA to treat Crohn's disease. (Doc. 188-6, p. 18). On May 14, 2015, at age 39, Mr. Blackburn's physician diagnosed Mr. Blackburn with chronic interstitial nephritis and stage four chronic kidney disease. (Doc. 188-8, p. 3). Mr. Blackburn contends that his use of LIALDA caused these conditions.

Shire has always warned that use of LIALDA could lead to kidney damage. In January of 2007, when the FDA initially approved LIALDA, the drug's label included the following information:

> **Renal:** Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine medications and prodrugs of mesalamine. For any patient with known renal dysfunction, caution should be exercised and LIALDA should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment.

(Doc. 41-1, p. 5). In November of 2013, when Mr. Blackburn began taking LIALDA, the label stated:

> **5.1 Renal Impairment**
>
> Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been

> reported in patients given products such as LlALDA that contain mesalamine or are converted to mesalamine.
>
> It is recommended that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy. Exercise caution when using LIALDA in patients with known renal dysfunction or a history of renal disease.

(Doc. 41-2, p. 3).

Mr. Blackburn does not contend that Shire failed to warn of possible kidney injury when using LIALDA. Instead, Mr. Blackburn alleges that the recommended "periodic" evaluation "constitutes a defective and unsafe instruction for safe use of LIALDA." (Doc. 41, p. 4, ¶ 22). He contends that the term "periodic" as generally used in drug labels refers to either semi-annual or annual testing and that Shire's warning should have "provide[d] for blood testing of renal function at intervals necessary to reasonably protect patients from LIALDA's potential renal toxicity." (Doc. 41, p. 5, ¶¶ 22, 23, 25).

Mr. Blackburn contends that the language regarding testing for renal function in Shire's warning should resemble language used by other manufacturers of mesalamine-based drugs. PENTASA, like LIALDA, is a 5-aminosalicylic acid ("5-ASA") or mesalamine-based drug. In the United Kingdom, PENTASA is marketed with the warning that patients "should have renal function monitored, with serum creatinine levels measured prior to treatment start, every 3 months for the first year, then [every 6 months] for the next 4 years and annually

thereafter." (Doc. 175-8, p. 2). Similarly, OCTASA, another 5-ASA drug, is marketed in the United Kingdom with the following instruction:

> It is recommended that all patients have an evaluation of their renal function prior to initiation of Octasa therapy and repeatedly whilst on therapy. As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. Short monitoring intervals early after the start of Octasa therapy will discover rare acute renal reactions. In the absence of an acute renal reaction monitoring intervals can be extended to every 3 months and then annually after 5 years.

(Doc. 175-6, p. 2).

Mr. Blackburn asserts that an appropriate label for LIALDA, a mesalamine-based drug, should include instructions recommending "evaluation of renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year." (Doc. 41, p. 5, ¶¶ 23, 25). Mr. Blackburn contends that Shire's failure to include this testing regimen in the LIALDA package warning in the fall of 2013 proximately caused his kidney injury. (Doc. 41, p. 5, ¶ 26). Embedded within this causation contention are the suppositions that the physician who prescribed LIALDA for Mr. Blackburn, Dr. Dino Ferrante, would have ordered specific interval testing per the instructions that Mr. Blackburn proposes and that Mr. Blackburn would

have complied with those orders. Mr. Blackburn's medical history undermines those suppositions.

Mr. Blackburn first saw Dr. Ferrante at the Center for Colon & Digestive Disease on September 6, 2013 based on a referral from Dr. Craig Young. (Doc. 162-1, p. 5, tr. 17; Doc. 188-6, pp. 12-13). In his deposition, Dr. Ferrante testified:

> [Dr. Young] called me personally first before I saw [Mr. Blackburn], said I'm sending you this guy, Mark Blackburn. He's having some loose bowels, diarrhea. We talked about him a little bit. [Dr. Young] said he had done some basic workup ..., some blood work, I think some stool tests, possibly, and everything checked out okay and he wanted me to do some further gastrointestinal evaluation in regards to his symptoms, which the main one being he was having, basically, diarrhea or loose bowel movements.

(Doc. 162-1, p. 5, tr. 18).

At his initial visit with Dr. Ferrante, Mr. Blackburn complained of "diarrhea or alteration of his stools" and "urgency," without abdominal pain, bleeding, or fever. (Doc. 162-1, p. 5, tr. 20). Dr. Ferrante stated:

> So based on his symptoms, we decided to do what's called a C-reactive protein, which is an inflammatory marker, looking for—we use it as a marker for inflammatory bowel disease. The tissue transglutaminase level is a marker of celiac disease. So, again, these are—we're checking for what causes loose bowels, and so these are two markers of

> things that are fairly common. And then, of course, we set him up for a colonoscopy to assess for his symptoms.

(Doc. 162-1, p. 6, tr. 22). Mr. Blackburn's lab work was normal. (Doc. 162-1, p. 7, tr. 26). The colonoscopy revealed "chronic colitis," otherwise known as "inflammation of the colon," and "non-caseating granulomas," which are "diagnostic for Crohn's disease." (Doc. 162-1, p. 9, tr. 34). Dr. Ferrante was not sure whether Mr. Blackburn had Crohn's disease or ulcerative colitis, so he scheduled Mr. Blackburn for a sigmoidoscopy. (Doc. 162-1, p. 9, tr. 36). That procedure revealed "caseating granulomas." (Doc. 162-1, p. 11, tr. 41-42). Dr. Ferrante also ordered blood tests to rule out ulcerative colitis. (Doc. 162-1, p. 10, tr. 37). Based on the results of these tests, Dr. Ferrante diagnosed Mr. Blackburn with Crohn's disease. (Doc. 162-1, pp. 11, 14, tr. 42, 55).

On November 5, 2013, Dr. Ferrante prescribed LIALDA and gave Mr. Blackburn an initial prescription for a six-month course of treatment. (Doc. 162-1, pp. 14, 30, tr. 55, 117; Doc. 188-6, p. 18). Dr. Ferrante acknowledged that prescribing LIALDA for Crohn's disease was an off-label use of the product. (Doc. 162-1, p. 27, tr. 108). Dr. Ferrante stated, "you want to tailor your therapy based on the individual." (Doc. 162-1, p. 19, tr. 73). In Dr. Ferrante's opinion, "a mesalamine product" such as LIALDA was the "drug of choice" for Mr. Blackburn "because it's the least invasive ... and probably easiest to administer in someone who would be traveling," like Mr. Blackburn. (Doc. 162-1, p. 19, tr. 73). The alternative would have been "either oral medications that do require some

monitoring or IV infusion therapies which require even more intensive type monitoring." (Doc. 162-1, p. 19, tr. 73; *see also* Doc. 162-1, p. 19, tr. 74).

Dr. Ferrante was aware when he prescribed LIALDA to Mr. Blackburn that mesalamine products contain warnings that "renal impairment may occur" and directions to "assess renal function at the beginning of treatment and periodically during treatment." (Doc. 162-1, pp. 15-16, tr. 60-61).[2] But Dr. Ferrante did not look at the LIALDA label before he prescribed the drug to Mr. Blackburn. (Doc. 162-1, p. 24, tr. 93).

Dr. Ferrante testified that before prescribing any medication "if there's anything that needs to be checked prior, we will typically do that." (Doc. 162-1, p. 15, tr. 59). Then, "during the follow-up process, I will ask [patients], you know, how they're doing on the medication." (Doc. 162-1, p. 15, tr. 59). Dr. Ferrante testified that he would have relied on discussions with Mr. Blackburn. (Doc. 162-1, p. 17, tr. 67). Dr. Ferrante stated: "I usually ask have you had blood work done

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[2] Quoting the exact language from the LIALDA warning, counsel asked Dr. Ferrante if he knew that:

> renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and rarely, renal failure, has been reported in patients given products such as LlALDA that contain mesalamine or are converted to mesalamine.

(Doc. 162-1, p. 23, tr. 92). Dr. Ferrante stated that he was aware of these problems and stated that he had been aware "for some time prior to prescribing LIALDA for Mr. Blackburn" because "that language had been in labeling for mesalamine products in the United States for a long period of time." (Doc. 162-1, pp. 23-24, tr. 92-93).

by your primary care doctor before you came here or any other doctor, and if the answer is no, then I'll take it upon myself to go ahead and check that." (Doc. 162-1, p. 17, tr. 67). But Dr. Ferrante did not evaluate Mr. Blackburn's renal function before he prescribed LIALDA for him, and when he selected LIALDA for Mr. Blackburn, Dr. Ferrante did not know whether Dr. Young had performed renal testing on Mr. Blackburn. (Doc. 162-1, p. 23, tr. 91).

Dr. Ferrante testified that he ordinarily checked renal function "at least once a year" when prescribing LIALDA. (Doc. 162-1, pp. 15-16, tr. 60-61). When asked in his deposition what "periodically" means to him, to Dr. Ferrante responded:

> Currently, I'm doing one year. This condition, like Crohn's disease, ulcerative colitis, is typically a condition in younger patients, so most of the time, they don't have a lot of other medical conditions. So I think once a year is probably adequate in those patients. If it's a patient who has other medical conditions, I might be more aggressive with that. Most of the time, these patients also come from their primary care doctor or some other doctor being referred, and they may have already had or are getting yearly testing or biyearly testing for other reasons.

(Doc. 162-1, p. 16, tr. 61-62). Later in his deposition Dr. Ferrante acknowledged that "periodically" can mean other time periods as well and that there is no specific definition of "periodically" in the medical profession. (Doc. 162-1, p. 23, tr. 90). Dr. Ferrante explained that in his 17 years of practice he had "never

seen kidney problems from these [mesalamine] medications." (Doc. 162-1, p. 28, tr. 109-110).

To understand a medication's side effects, Dr. Ferrante relies on mailers from drug companies, conferences, and drug company representatives. (Doc. 162-1, p. 16, tr. 62-63). When asked in his deposition what he relied on "for information, data, and guidance on instructions for safe use of medications such as Lialda," Dr. Ferrante responded:

> typically, like the package insert, if you will, of the medicines. I mean, we're pretty well trained on what's the most common side effects, adverse reactions. If anything new comes out, many times, again, that comes out as a mailer, actually. We have seen that in other medications before.

(Doc. 162-1 pp. 16-17, tr. 64-65). In his deposition, Dr. Ferrante reviewed the LIALDA warning in place when he prescribed the medication to Mr. Blackburn. (Doc. 162-1, p. 17, tr. 65). The following exchange then took place:

> Q. ... [I]s this information the type of information you rely on in determining whether a medication is appropriate for your patient?
>
> * * *
>
> A. Yes. We would look at—before we start a medicine, we'd want to make sure that they would be a good candidate for that medication, sure.
>
> Q. Is this information also the type of data you rely on in determining what safe use

> protocol or testing recommendations you give your patients?
>
> * * *
>
> A. Correct.
>
> Q. And did you rely on this information when determining [if] you want[ed] to prescribe Lialda for Mark Blackburn?
>
> * * *
>
> A. Yes.

(Doc. 162-1, p. 17, tr. 65-66). During his deposition, Dr. Ferrante also reviewed the PENTASA and OCTASA monitoring language set out above. (Doc. 162-1, p. 18, tr. 69-72). Dr. Ferrante averred that if the LIALDA label had had similar language, and he had known about it, he "would have followed those protocols." (Doc. 162-1, p. 18, tr. 71-72; *see also* Doc. 162-1, p. 20, tr. 77 ("Again, if I would have known about that, I would have followed those protocols."); Doc. 162-1, p. 24, tr. 95 ("If I would have known about that protocol, then yes.")).

After prescribing LIALDA, Dr. Ferrante did not tell Mr. Blackburn to come back for renal testing. (Doc. 162-1, pp. 17-18, tr. 68-69). Dr. Ferrante believes that his office scheduled Mr. Blackburn to return on January 14, 2014. (Doc. 162-1, pp. 12, 14, 29, tr. 45, 47, 53, 113). That visit would have been a follow-up to gauge the effectiveness of the LIALDA therapy and the side effects of the medication. (Doc. 162-1, p. 12, tr. 47-48). Mr. Blackburn did not keep that appointment, and Dr. Ferrante never saw Mr. Blackburn again. (Doc. 162-1, p. 29, 114).

Despite Mr. Blackburn having missed his only follow-up appointment and despite having not seen Mr. Blackburn for almost 18 months, on March 6, 2015, Dr. Ferrante's office approved a new four-month prescription of LIALDA for Mr. Blackburn. (Doc. 188-6, p. 19). Dr. Ferrante did not know that his office had given Mr. Blackburn this new prescription. (Doc. 162-1, p. 30, tr. 117) ("I'm not aware of that. I don't know if he got that through our office. Maybe he called or—you know, I'm not aware of that. I don't remember seeing anything about that.").

ANALYSIS

Mr. Blackburn's remaining claim against Shire is for "strict liability for failure to warn" under the Alabama Extended Manufacturer's Liability Doctrine—the AEMLD. (Doc. 41, pp. 25-28). Under the AEMLD, "'a manufacturer, or supplier, or seller, who markets a product not reasonably safe when applied to its intended use in the usual and customary manner, [is] negligen[t] as a matter of law.'" *DISA Indus., Inc. v. Bell*, 272 So. 3d 142, 149 (Ala. 2018), *reh'g denied* (Sept. 14, 2018) (quoting *Casrell v. Altec Indus., Inc.*, 335 So. 2d 128, 132 (Ala. 1976)) (emphasis in *DISA*). Alabama law deems prescription drugs "unavoidably unsafe." *Stone v. Smith, Kline & French Labs.*, 447 So. 2d 1301, 1304 (Ala. 1984). Accordingly, "'the adequacy of the accompanying warning determines whether the drug, as marketed, is defective, or unreasonably dangerous.'" *Bodie v. Purdue Pharma Co.*, 236 Fed. Appx. 511, 518 (11th Cir. 2007) (quoting *Stone*, 447 So. 2d at 1304).

In Alabama, "[a] prescription-drug manufacturer fulfills its duty to warn the ultimate users of the risks

of its product by providing adequate warnings to the learned intermediaries who prescribe the drug." *Wyeth, Inc. v. Weeks*, 159 So. 3d 649, 673 (Ala. 2014). The Alabama Supreme Court has explained:

> The principle behind the learned-intermediary doctrine is that prescribing physicians act as learned intermediaries between a manufacturer of a drug and the consumer/patient and that, therefore, the physician stands in the best position to evaluate a patient's needs and to assess the risks and benefits of a particular course of treatment for the patient. A consumer can obtain a prescription drug only through a physician or other qualified health-care provider. Physicians are trained to understand the highly technical warnings required by the FDA in drug labeling.

Weeks, 159 So. 3d at 672-73 (citations omitted). The doctrine "recognizes the role of the physician as a learned intermediary between a drug manufacturer and a patient." *Weeks*, 159 So. 3d at 673.

"'[T]he adequacy of [a drug manufacturer's] warning is measured by its effect on the physician, to whom it owe[s] a duty to warn, and not by its effect on the consumer." *Weeks*, 159 So. 3d at 673 (quoting *Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313-14 (11th Cir. 2000)) (citations, quotations and changes omitted).

> Once the manufacturer has met its duty to warn, the manufacturer holds no further duty to warn the patient directly. *See Weeks*, 159 So. 3d at 673. If, however, the warning to the

> learned intermediary is insufficient or is a misrepresentation of risks, "the manufacturer remains liable for the injuries sustained by the patient." *Id*. In such a situation, the patient must show that:
>
> > the manufacturer failed to warn the physician of a risk not otherwise known to the physician and that the failure to warn was the actual and proximate cause of the patient's injury. In short, the patient must show that, but for the false representation made [or the insufficient information provided] in the warning, the prescribing physician would not have prescribed the medication to his patient.
>
> *Id.* at 673-74.

Tutwiler v. Sandoz, Inc., 726 Fed. Appx. 753, 756 (11th Cir. 2018). "[P]roof of proximate cause could [also] 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 U.S., Inc.*, No. 2:16-CV-963-RDP, 2017 WL 1833524 at *8 (May 8, 2017) (citing *Barnhill v. Teva Pharm, USA, Inc.*, 819 F. Supp. 2d 1254, 1261 (S.D. Ala. 2011); and *Fields v. Eli Lilly & Co.*, 116 F. Supp. 3d 1295, 1307 (M.D. Ala. 2015)).

If an alternative warning would not have impacted a prescribing physician's conduct in the use and monitoring of a drug, then a plaintiff cannot

establish the causation element for a products liability claim against the drug's manufacturer. Under Alabama law, in warnings cases concerning a prescription drug, plaintiffs:

> must demonstrate a causal link between the allegedly inadequate warning and the injury. In cases such as these, that means that the plaintiffs must demonstrate that, had the [drug manufacturer] given an adequate warning, it would have been read and heeded by the prescribing physicians.

Brasher v. Sandoz Pharm. Corp., No. CV 98-TMP-2648-S, 2001 WL 36403362, at *13 (N.D. Ala. Sept. 21, 2001) (citing *Gurley v. American Honda Mtr. Co.*, 505 So. 2d 358, 361 (Ala. 1987)); *see also*, *Wyeth*, 159 So. 3d at 677 n.11 ("[W]e are not deciding the merits of the underlying case. It may be that a jury finds that ... [the] physician did not rely on the warnings on the label[.]"); *see also Wyeth*, 159 So. 3d at 681 (Moore, dissenting) ("For example, if [the] prescribing physician did not rely on the ... labeling when prescribing the drug, then the [plaintiffs] will have failed to prove causation and their claims will fail.").

A drug manufacturer is entitled to judgment as a matter of law on a warnings claim when the record demonstrates that the prescribing physician would not have read or followed an alternative warning. *Bodie v. Purdue Pharma Co.*, 236 Fed. Appx. 511, 521 (11th Cir. 2007) ("Because the evidence suggests that the learned intermediary, Dr. Mangieri, prescribed OxyContin based on his independent knowledge of the drug and its high potential for addiction, we cannot conclude that the allegedly inadequate warning (that

is, the claimed defect) proximately caused Bodie's injury of addiction."); *Emody v. Medtronic, Inc.*, 238 F. Supp. 2d 1291, 1296 (N.D. Ala. 2003) (failure to warn claim failed in light of doctor's testimony that he did not rely on warnings); *In re Wright Med. Tech. Inc., Conserve Hip Implant Prod. Liab. Litig.*, 127 F. Supp. 3d 1306, 1359 (N.D. Ga. 2015) ("[W]here a warning is provided, but a physician does not read it or rely on it, a person cannot assert a failure to warn claim, even if the warning is defective."); *Salyards ex rel. Salyards v. Metso Minerals Tamper OY*, No. 1:04 CV 05798 OWW LJ, 2005 WL 3021959, at *9 (E.D. Cal. Nov. 10, 2005) ("If the doctor fails to read or heed the warning, the manufacturer is absolved of liability."). There is no presumption in Alabama that an adequate warning would have been read and heeded by the prescribing physician. *Barnhill* 819 F. Supp. 2d at 1262. "[A]s concerns proximate cause, a negligent-failure-to-warn-adequately case should not be submitted to the jury unless there is substantial evidence that an adequate warning would have been read and heeded and would have prevented the [injury]." *Deere & Co. v. Grose*, 586 So. 2d 196, 198 (Ala. 1991) (citing *Gurley*, 505 So. 2d at 361).

Here, the evidence demonstrates that Dr. Ferrante did not follow the instructions that Shire provided in November 2013 for renal evaluation when prescribing LIALDA, so Mr. Blackburn cannot prove that Dr. Ferrante would have read and heeded an alternative instruction. It is undisputed that Shire warned that LIALDA could cause interstitial nephritis and kidney disease, the conditions Mr. Blackburn claims he developed after taking the drug. Dr. Ferrante testified that he had been aware for some

time that 5-ASA drugs such as LIALDA could cause these conditions. He prescribed the drug to Mr. Blackburn anyway because LIALDA was the "drug of choice ... because it's the least invasive ... and probably easiest to administer in someone [like Mr. Blackburn] who would be traveling." (Doc. 162-1, p. 19, tr. 73). Dr. Ferrante prescribed LIALDA for Mr. Blackburn because the drug required less monitoring and had fewer serious side effects than alternative treatments for Crohn's disease. (Doc. 162-1, p. 19, tr. 73-74).

In November 2013, Shire "recommended" to prescribing physicians "that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy." (Doc. 41-2, p. 3). But Dr. Ferrante did not read this information before he prescribed LIALDA to treat Mr. Blackburn's Crohn's disease, an off-label use of the drug. And Dr. Ferrante neither ordered tests to evaluate Mr. Blackburn's renal function before he prescribed LIALDA nor checked with Mr. Blackburn's referring physician, Dr. Young, to determine whether Dr. Young had evaluated Mr. Blackburn's renal function. (Doc. 162-1, p. 23, tr. 91). And though Dr. Ferrante testified that it was his practice to test renal function annually when prescribing LIALDA (Doc. 162-1, p. 16, tr. 61-62), his office authorized CVS to refill Mr. Blackburn's November 2013 prescription in March 2015 without conducting a renal evaluation of Mr. Blackburn. (Doc. 188-6, p. 19). Dr. Ferrante's inattention to Shire's November 2013 renal evaluation protocol may stem from the fact that in 17 years of practice as a gastroenterologist, Dr. Ferrante had "never seen kidney problems" from mesalamine products. (Doc. 162-1, p. 28, tr. 109-110).

Even if Dr. Ferrante had ordered a renal evaluation of Mr. Blackburn after prescribing LIALDA, there is no evidence that Mr. Blackburn would have complied with the instruction. Dr. Ferrante scheduled an appointment with Mr. Blackburn in January 2014 to monitor Mr. Blackburn's treatment, but Mr. Blackburn did not keep the appointment. After Dr. Ferrante prescribed LIALDA for Mr. Blackburn in November 2013, Mr. Blackburn did not return to Dr. Ferrante.

Mr. Blackburn correctly points out that Dr. Ferrante testified that he would have followed an alternative recommended testing schedule if he "had known about it." (Doc. 162-1, p. 18, tr. 71-72; see also Doc. 162-1, p. 20, tr. 77; Doc. 162-1, p. 24, tr. 95). But that testimony amounts to unsubstantiated speculation, given Dr. Ferrante's conduct, and a jury verdict may not rest on speculation. *See Pennsylvania R. Co. v. Chamberlin*, 288 U.S. 333, 340-44 (1933) ("And the desired inference is precluded for the further reason that respondent's right of recovery depends upon the existence of a particular fact which must be inferred from proven facts, and this is not permissible in the face of the positive and otherwise uncontradicted testimony of unimpeached witnesses consistent with the facts actually proved, from which testimony it affirmatively appears that the fact sought to be inferred did not exist ... Leaving out of consideration, then, the inference relied upon, the case for respondent is left without any substantial support in the evidence, and a verdict in her favor would have rested upon mere speculation and conjecture. This, of course, is inadmissible.") (internal marks and citations omitted).

Because Dr. Ferrante did not consult Shire's November 2013 warning before prescribing the drug, the Court does not have to accept his self-interested statement that he would read an alternative warning or that a different warning would have altered his decision to prescribe LIALDA without evaluating Mr. Blackburn's renal function. In a decision that is binding precedent in the Eleventh Circuit Court of Appeals, the Fifth Circuit Court of Appeals explained:

> [S]elf-serving statements alone do not create a jury question:
>
> > In our opinion, the isolated self-serving statements of the Cal-Florida officers were not enough to constitute substantial evidence for the jury on the causation issue under Boeing Co. v. Shipman.
>
> *Yoder Bros., Inc. v. California-Florida Plant Corp.*, 537 F.2d 1347, 1371 (5th Cir. 1976). A trier of facts need not ignore powerful self-interest, and where there is no relevant support for self-interested testimony a jury must not be allowed to speculate as to causation. A directed verdict, or judgment notwithstanding the verdict, is the proper safeguard against such speculation by the jury ...

Ralston Purina Co. v. Hobson, 554 F.2d 225, 729 (5th Cir. 1977) (footnotes omitted).[3] A summary judgment

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[3] *Bonner v. City of Prichard*, 661 F.2d 1206, 1209 (11th Cir. 1981) (adopting as binding precedent in the Eleventh Circuit

likewise safeguards against a jury verdict based on a non-party witness's self-interested, speculative testimony regarding causation that is wholly contradicted by historical fact. This is not the type of evidence that creates a question of disputed fact for a jury to resolve.[4]

And even if a jury could consider Dr. Ferrante's testimony, Mr. Blackburn's failure to keep his January 2014 appointment and follow up with Dr. Ferrante severs the causal chain. In the absence of admissible evidence of a causal link between Shire's instructions for renal evaluations when prescribing

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Court of Appeals decisions that the Fifth Circuit Court of Appeals rendered before October 1, 1981).

[4] When considering a summary judgment motion, a district court must view the evidence in the record and draw reasonable inferences from the evidence in the light most favorable to the non-moving party. *Asalde v. First Class Parking Sys. LLC*, 898 F.3d 1136, 1138 (11th Cir. 2018). "A litigant's self-serving statements based on personal knowledge or observation can defeat summary judgment." *United States v. Stein*, 881 F.3d 853, 857 (11th Cir. 2018); see also *Feliciano v. City of Miami Beach*, 707 F.3d 1244, 1253 (11th Cir. 2013) ("To be sure, Feliciano's sworn statements are self-serving, but that alone does not permit us to disregard them at the summary judgment stage."). The self-serving statements of a non-party witness do not have the same power when that witness's conduct directly contradicts his self-interested projections of future conduct, rendering those projections unsubstantiated speculation. A district court does not have to draw favorable inferences from speculation. *Daniels v. Twin Oaks Nursing Home,* 692 F.2d 1321, 1324 (11th Cir. 1982) ("[A]n inference is not reasonable if it is 'only a guess or a possibility,' for such an inference is not based on the evidence but is pure conjecture and speculation.") (internal citation omitted).

LIALDA and Mr. Blackburn's injury, Mr. Blackburn's AEMLD warnings claim against Shire must fail.

CONCLUSION

By separate order, for the reasons discussed above, the Court will enter judgment for the Shire defendants on Mr. Blackburn's AEMLD failure to warn claim as a matter of law. Because that is the only remaining claim in this case, the Court will dismiss this case with prejudice. The Court thanks the parties for their excellent briefs and oral argument. The issues in this case were fully explored and presented carefully for consideration. This decision renders moot the pending motions *in limine*.

In light of the public health emergency caused by the COVID-19 virus, the parties are reminded that under Rule 4(a)(5) of the Federal Rules of Appellate Procedure, a party may request an extension of time for a notice of appeal. In addition, pursuant to Rule 4(a)(6), a party may ask a district court to reopen the time to file a notice of appeal for 14 days. Parties are advised to study these rules carefully if exigent circumstances created by the COVID-19 public health emergency require motions under FRAP 4(a)(5) or 4(a)(6).

DONE and **ORDERED** this June 01, 2020.

[handwritten: signature]

MADELINE HUGHES HAIKALA

UNITED STATES DISTRICT JUDGE

Appendix F

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA

No. 2:16-CV-00963

MARK BLACKBURN,

Plaintiff,

v.

SHIRE U.S., INC., et al.,

Defendants.

Filed: May 10, 2018

MEMORANDUM OPINION

I. Introduction

This matter is before the court on Plaintiff's Motion to Reinstate Shire Development LLC as a Party Defendant (Doc. # 79) and Plaintiff's Motion for Reconsideration (Doc. # 91). Both the Motion to Reinstate (Docs. # 79, 81, 82) and the Motion for Reconsideration (Docs. # 91, 94, 96) are fully briefed. For the reasons stated below, the Motion to Reinstate (Doc. # 79) is due to be denied, and the Motion for Reconsideration (Doc. # 91) is due to be denied.

II. Background

Defendants Shire US Inc. and Shire LLC engage in the distribution, marketing, and sale of the drug known as Lialda. (Doc. # 41 at ¶ 8). In November 2013, Plaintiff was prescribed Lialda for treatment of his Crohn's disease. (*Id.* at ¶ 39). Plaintiff took Lialda, as prescribed, from November 2013 until February 2015. (*Id.*). In September 2015, Plaintiff was diagnosed with Stage IV renal failure and severe chronic interstitial nephritis. (*Id.* at ¶ 45). On June 10, 2016, Plaintiff filed a complaint against Shire US Inc., Shire LLC, Shire Development LLC, Shire Pharmaceutical Development, Inc., and Shire Pharmaceuticals LLC. (Doc. # 1).

On October 5, 2016, Defendants moved to dismiss Plaintiff's claims. (Docs. # 26, 27). Plaintiff filed an opposed motion to amend his complaint on October 24, 2016. (Doc. # 36). After the court ordered Defendants to file a brief in support of its opposition to Plaintiff's motion to amend (Docs. # 37-38), the court granted Plaintiff leave to amend on November 1, 2016. (Doc. # 40). On November 2, 2016, Plaintiff filed a First Amended Complaint. (Doc. # 41). In that amended pleading, Plaintiff asserted that Defendants' recommendation of only "periodic" renal testing while using Lialda, as opposed to the more specific testing regimen detailed in his First Amended Complaint, proximately caused his kidney injury. (*Id.* # 41 at ¶ 26). Specifically, Plaintiff asserted claims for failure to warn under the Alabama Extended Manufacturers Liability Doctrine ("AEMLD") (Count One), fraud (Count Two), suppression and concealment (Count

Three), and breach of express warranty (Count Four). (Doc. # 41).

On November 16, 2016, Defendants moved to dismiss Plaintiff's First Amended Complaint. (Docs. # 44, 45). On May 8, 2017, the court dismissed Counts Two, Three, and Four with prejudice and denied Defendants' motion to dismiss Count One without prejudice. (Docs. # 53, 54). After granting Defendants' motion to dismiss for lack of personal jurisdiction on May 12, 2017, the court dismissed Defendants Shire Development LLC, Shire Pharmaceutical Development, Inc., and Shire Pharmaceuticals LLC without prejudice. (Doc. # 56). On June 29, 2017, Plaintiff filed a Motion to Alter or Amend Order and Motion to Amend Complaint (Doc. # 64), which the court denied. (Docs. # 85, 86).

Plaintiff's Motion to Reinstate Shire Development LLC as a Party Defendant (Doc. # 79) and Plaintiff's Motion for Reconsideration (Doc. # 91) are currently pending before the court. In the Motion to Reinstate, Plaintiff argues that the court should grant him leave to amend his complaint to add Shire Development LLC as a defendant in this case because Shire Development LLC is the holder of the New Drug Application ("NDA") for Lialda. (Doc. # 79). In the Motion for Reconsideration, Plaintiff asks the court to reconsider its denial (Docs. # 85, 86) of his Motion to Alter or Amend Order (Doc. # 64) and to allow Plaintiff to file a Second Amended Complaint. (Doc. # 91). During an on-the-record conference held on November 16, 2017, the court asked the parties to brief Plaintiff's Motion for Reconsideration so that the court, at Plaintiff's request, could take a fresh look at Plaintiff's

proposed Second Amended Complaint (Doc. # 64-1). (Doc. # 94-1 at p. 30). The court explores the merits of both pending motions, which are essentially motions to amend, in turn.

III. Standard of Review

Rule 15 of the Federal Rules of Civil Procedure governs amended and supplemental pleadings. Absent circumstances not relevant here, a party may amend the pleadings only by leave of the court or by written consent of the adverse party. *See* Fed R. Civ P. 15(a)(2). "The court should freely give leave when justice so requires." *Id*. "Ordinarily, a party must be given at least one opportunity to amend before the district court dismisses the complaint." *See Corsello v. Lincare, Inc.*, 428 F.3d 1008, 1014 (11th Cir. 2005). That is, "[u]nless a substantial reason exists to deny leave to amend, the discretion of the District Court is not broad enough to permit denial." *Fla. Evergreen Foliage v. E.I. DuPont De Nemours and Co.*, 470 F.3d 1036, 1041 (11th Cir. 2006) (quotation marks omitted).

The court, however, need not allow an amendment that would be futile. *See Bryant v. Dupree*, 252 F.3d 1161, 1163 (11th Cir. 2001). An amendment is futile when "the complaint as amended is still subject to dismissal." *Hall v. United Insurance Co.*, 367 F.3d 1255, 1263 (11th Cir. 2004) (citing *Burger King Corp. v. Weaver*, 169 F.3d 1310, 1320 (11th Cir. 1999)). A court also need not allow an amendment where there has been undue delay, bad faith, dilatory motive, or repeated failure to cure deficiencies by amendments previously allowed or where allowing the amendment would cause undue prejudice to the opposing party. *See Halpin v. Crist*, 405 Fed. App'x

403, 408-09 (11th Cir. 2010) (quoting *Corsello*, 428 F.3d at 1014); *see also Maynard v. Bd. of Regents of Div. of Univs.*, 342 F.3d 1281, 1287 (11th Cir. 2003) (holding that the district court did not abuse its discretion in denying a motion to amend filed on the last day of discovery because granting the motion "would have produced more attempts at discovery, delayed disposition of the case, likely prejudice ... [and] there seems to be no good reason why [the movant] could not have made the motion earlier"). A district court may, in the exercise of its inherent power to manage the conduct of litigation before it, deny leave to amend a complaint, "so long as it does not outright refuse to grant the leave without any justifying reason." *Equal Rights Center v. Niles Bolton Assocs.*, 602 F.3d 597, 603 (4th Cir. 2010); *see also Reese v. Herbert*, 527 F.3d 1253, 1263 (11th Cir. 2008).

IV. Analysis

As explained below, because all of Plaintiff's proposed amendments would be futile, both motions are due to be denied. *See Bryant*, 252 F.3d at 1163.

A. Motion for Reconsideration

As an initial matter, and as more fully detailed in the court's prior Memorandum Opinion (Doc. # 85) denying Plaintiff's Motion to Alter or Amend Order (Doc. # 64), a plaintiff represented by counsel is not entitled to the opportunity to amend his complaint without leave of court or agreement of opposing counsel when the plaintiff has already previously amended his complaint. *See Eiber Radiology, Inc. v. Toshiba Am. Med. Sys., Inc.*, 673 F. App'x 925, 930 (11th Cir. 2016) ("[The Eleventh Circuit has] never required district courts to grant counseled plaintiffs

more than one opportunity to amend a deficient complaint, nor have we concluded that dismissal with prejudice is inappropriate where a counseled plaintiff has failed to cure a deficient pleading after having been offered ample opportunity to do so."); *see also Henley v. Turner Broad. Sys., Inc.*, 267 F. Supp. 3d 1341, 1364 (N.D. Ga. 2017) ("The Court also concludes it is unnecessary to allow Plaintiffs, who are represented by counsel, the opportunity to file a further amended complaint."). Although the court explained to Plaintiff's counsel why his proposed Second Amended Complaint was futile, the court permitted the parties to brief Plaintiff's Motion for Reconsideration. (*See* Doc. # 94-1). The court now (and, once again) explains why Plaintiff's proposed Second Amended Complaint does not cure the deficiencies the court recognized in its previous Memorandum Opinion (Doc. # 53) dismissing Plaintiff's breach of express warranty and fraud-based claims.

1. The Proposed Second Amended Complaint Does Not Cure Plaintiff's Breach of Express Warranty Claim

Plaintiff claims that his Second Amended Complaint properly states a breach of express warranty claim. (Doc. # 96 at p. 8). The proposed Second Amended Complaint points to § 5.1 of the Warnings and Precautions in the 2013 Label and contends that this section provides instructions for safe use that form the basis of the bargain. (Docs. # 64-1 at ¶¶ 268-79; 96 at p. 9). Defendants counter that the additional language in the proposed Second Amended Complaint referencing § 5.1 of the 2013

Label do not alter Plaintiff's breach of express warranty allegation contained in his First Amended Complaint. (Doc. # 94 at p. 22-23). The court agrees with Defendants. The court has already examined the 2013 Label in the context of a breach of express warranty claim and found that the 2013 Label "cannot to be construed as an express warranty of safeness." (Doc. # 53 at p. 17-18). The court further noted that, to the extent that the Lialda Label could be construed as a description of goods, its "description" is contrary to an express warranty for safeness because it expressly states that its use may cause a number of side effects. (*Id.* at p. 18). Plaintiff's additional language in the proposed Second Amended Complaint highlighting § 5.1 of the 2013 Label does not change this conclusion. Rather, the proposed amendment simply highlights language that the court has already considered. (*Compare* Doc. # 64-1 at ¶¶ 268-79 *with* Doc. # 53 at p. 17-18). As such, Plaintiff's proposed amended breach of express warranty claim does not cure the deficiencies noted in the court's Memorandum Opinion (Doc. # 53 at p. 17-18) and is futile. *See Hall*, 367 F.3d at 1263.

2. The Proposed Second Amended Complaint Does Not Cure Plaintiff's Fraud-Based Claims

The court previously dismissed Plaintiff's fraud-based claims in his First Amended Complaint because these claims "failed to plead the existence of a *material fact* to support [those] claims." (Doc. # 53 at p. 19) (emphasis in original). The court also noted that if Plaintiff had alleged that Defendants (1) "misrepresented (or concealed) the existence of

certain adverse events or potential side effects of LIALDA" or (2) "made a 'sales pitch' or other representation regarding the safety of its recommended 'periodic' renal testing regimen.," then the court's analysis of these fraud-based claims may be different. (*Id.* at p. 19-20). But Plaintiff has not sufficiently made either of these allegations in his proposed Second Amended Complaint. Rather, Plaintiff argues that his proposed Second Amended Complaint cures the deficiencies of his fraud-based claims from his First Amended Complaint because it "explain[s] in detail why § 5.1 of the 2013 Label is a legally mandated statement of instructions for safe use and a material misrepresentation regarding safe use." (Doc. # 65 at p. 10) (citing Doc. # 64-1 at ¶¶ 188-205).

A fraud claim must comply with Federal Rule of Civil Procedure 9(b). Rule 9(b) requires that a party alleging fraud to "state with particularity the circumstances constituting fraud." Fed. R. Civ. P. 9(b). Under Rule 9(b), "a plaintiff must allege: '(1) the precise statements, documents, or misrepresentations made; (2) the time, place, and person responsible for the statement; (3) the content and manner in which these statements misled the Plaintiffs; and (4) what the defendants gained by the alleged fraud.'" *Am. Dental Ass'n v. Cigna Corp.*, 605 F.3d 1283, 1291 (11th Cir. 2010) (quoting *Brooks v. Blue Cross & Blue Shield of Fla., Inc.*, 116 F.3d 1364, 1380-81 (11th Cir. 1997)). Of course, the heightened pleading requirements of Rule 9(b) must also satisfy the plausibility mandate set forth in *Twombly* and *Iqbal*. Plaintiff has failed to satisfy either requirement—in both his First Amended Complaint and Second Amended Complaint.

In order to proceed on his fraud claim, Plaintiff must plausibly plead (1) a false representation (2) of a material existing fact (3) relied upon by the plaintiff (4) who was damaged as a proximate result of the misrepresentation. *Coastal Concrete Co. v. Patterson*, 503 So. 2d 824, 826 (Ala. 1987). To proceed on his fraudulent suppression claim, Plaintiff must plausibly plead the existence of the following elements: "(1) a duty on the part of the defendant to disclose facts; (2) concealment or nondisclosure of material facts by the defendant; (3) inducement of the plaintiff to act; (4) action by the plaintiff to his or her injury." *Lambert v. Mail Handlers Ben. Plan*, 682 So. 2d 61, 63 (Ala. 1996). "In Alabama, a drug manufacturer 'may be held liable for fraud or misrepresentation (by misstatement or omission)' based on 'information and warning deficiencies' on a drug's labelling." *Houston v. Bayer Healthcare Pharm., Inc.*, 16 F. Supp. 3d 1341, 1350 (N.D. Ala. 2014) (quoting *Wyeth, Inc. v. Weeks*, 159 So. 3d 649, 676 (Ala. 2014)). More specifically, a plaintiff "can base her fraud and misrepresentation claims on the defendant manufacturer's breach of its 'duty to warn ... *about the risks associated with the long-term use of the drug' in its labeling*." *Id.* (quoting *Weeks*, 159 So. 3d at 655-56).

In this case, Plaintiff's First Amended Complaint and Second Amended Complaint simply do not allege that Defendants failed to warn *about the risks* associated with the long-term use of Lialda in its labeling. (*See* Docs. # 41, 64-1). Indeed, there is no question that Lialda's labels warned that a consumer may develop kidney damage from use of the product (as Plaintiff did). (Docs. # 41 at ¶ 18; 64-1 at ¶ 15). Rather than asserting that Defendants failed to warn

about the risks associated with the use of Lialda, both complaints allege that the recommended "periodic" evaluation failed to provide information regarding the safe use of Lialda, including proper testing. (*See* Docs. # 41 at ¶ 22, 175, 183; 64-1 at ¶ 182). Ultimately, Plaintiff is attempting to transform Lialda's warning into a safety warranty in order to support its fraud-based claims. And, for the reasons explained in the court's Memorandum Opinion, the warnings contained in § 5.1 of the 2013 Label "cannot to be construed as an express warranty of safeness." (Doc. # 53 at p. 17-18).

The court agrees with Plaintiff that both AEMLD and fraud-based claims against drug manufactures can coexist under Alabama law (even if the substance of the fraud-based claim is essentially a products liability claim). *See Weeks*, 159 So. 3d at 656. However, that rule of law does not mean that a court cannot dismiss fraud-based claims that fail to satisfy the requirements of Rule 9(b) and the plausibility mandate set forth in *Twombly* and *Iqbal*.[1] As this court explained in its previous Memorandum Opinion when analyzing Plaintiff's fraud-based claims:

> While the court assumes the veracity of the facts contained within Plaintiff's amended

[1] In its Motion to Dismiss, Defendants argued that all of Plaintiff's claims are barred based on preemption and the Learned Intermediary Doctrine. (Doc. # 45 at p. 17-27). Additionally, Defendants specifically challenged elements of Plaintiff's breach of express warranty, fraud, and concealment claims but did not include a similar elements-based challenge for Plaintiff's failure to warn claim. (Doc. # 45 at p. 27-31). Accordingly, the court did not specifically address the sufficiency of Plaintiff's failure to warn claim under *Twombly* and *Iqbal*.

> complaint, the court is not required to afford "conclusions" or "naked assertion[s]" a presumption of truth when evaluating Defendants' motion to dismiss. *Twombly*, 550 U.S. at 555, 557. Here, Plaintiffs' assertion that LIALDA's label constituted a representation that LIALDA therapy would be safe is just such a conclusion. Moreover, it is a conclusion not supported by the facts in Plaintiff's amended complaint. Plaintiff attached LIALDA's 2013 label to his amended complaint. And, as addressed above, LIALDA's label addresses in detail a wide array of potential side effects that LIALDA users may endure and does not state that a LIALDA user would be free from injury if that user followed the label's recommended testing regimen.

(Doc. # 53 at p. 20 n.5). Plaintiff's proposed Second Amended Complaint continues to base its fraud-based claims on a naked assertion that the Lialda labels represented that Lialda therapy would be safe.[2] (Doc. # 64-1 at ¶ 170, 224). Therefore, the Second Amended Complaint does not cure the First Amended

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[2] The court notes that Plaintiff added language in his proposed Second Amended Complaint regarding Defendants' compliance with FDA regulations. (Doc. # 64-1 at ¶¶ 171-79). To the extent that Plaintiff is raising a claim that Defendants violated the FDCA, these claims are precluded by 21 USC § 337(a). *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4 (2001) ("The FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the medical device provisions ....").

Complaint's deficiencies related to Plaintiff's fraud-based claims and is futile. *See Hall*, 367 F.3d at 1263.

Plaintiff is not entitled to leave to amend his complaint as a matter of right yet another time. *See Wagner v. Daewoo Heavy Indus. Am. Corp.*, 314 F.3d 541, 542-44 (11th Cir. 2002). And, even if the court had dismissed these claims without prejudice (instead of with prejudice) and had granted Plaintiff leave to file his proposed Second Amended Complaint, the proposed amendments would be futile. Accordingly, the Motion for Reconsideration (Doc. # 91) is due to be denied.

B. Motion to Reinstate

Plaintiff contends that the court should grant him leave to amend his complaint to add Shire Development LLC as a defendant in this case because Shire Development LLC is the holder of the NDA for Lialda. (Doc. # 79). Defendants counter that such leave should not be granted because this court does not have personal jurisdiction over Shire Development LLC (Doc. # 81). For the reasons explained below, the court agrees with Defendants.

"A plaintiff seeking the exercise of personal jurisdiction over a nonresident defendant bears the initial burden of alleging in the complaint sufficient facts to make out a prima facie case of jurisdiction." *United Techs. Corp. v. Mazer*, 556 F.3d 1260, 1274 (11th Cir. 2009). In determining whether the exercise of personal jurisdiction over a nonresident defendant[3]

[3] It is undisputed that Shire Development LLC is incorporated in and has its principal place of business outside of Alabama, does not have any office or facilities in Alabama, and does not have a

is appropriate, the court first considers a state's long-arm statute. *See Cable/Home Communication Corp. v. Network Prods., Inc.*, 902 F.2d 829, 855 (11th Cir. 1990); *see also Alexander Proudfoot Co. World Headquarters L.P. v. Thayer*, 877 F.2d 912, 919 (11th Cir. 1989). Alabama's long-arm statute permits personal jurisdiction to the extent it "is not inconsistent with the constitution of this state or the Constitution of the United States." Ala. R. Civ. P. 4.2(b). Because Alabama's long-arm statute allows the exercise of personal jurisdiction to the full extent permissible under the U.S. Constitution, the court next determines whether sufficient minimum contacts exist to satisfy the Due Process Clause of the Fourteenth Amendment so that "maintenance of the suit does not offend 'traditional notions of fair play and substantial justice.'" *International Shoe Co. v. Washington*, 326 U.S. 310, 316 (1945) (quoting *Milliken v. Meyer*, 311 U.S. 457, 463 (1940)); *see also Cable/Home Communication Corp.*, 902 F.2d at 855; *Alexander Proudfoot Co.*, 877 F.2d at 919.

Plaintiff does not argue that this court has general jurisdiction over Shire Development LLC. Accordingly, the court focuses on whether it has specific jurisdiction over Shire Development LLC. As the Supreme Court has explained:

> In order for a state court to exercise specific jurisdiction, the *suit* must arise out of or relate to the defendant's contacts with the *forum*. In other words, there must be an

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registered agent for service of process in Alabama. (*See* Doc. # 43-1).

> affiliation between the forum and the underlying controversy, principally, an activity or an occurrence that takes place in the forum State and is therefore subject to the State's regulation. For this reason, specific jurisdiction is confined to adjudication of issues deriving from, or connected with, the very controversy that establishes jurisdiction.

Bristol-Myers Squibb Co. v. Superior Court of California, San Francisco Cty., 137 S. Ct. 1773, 1780 (2017) (emphasis in original) (internal citations, quotations, and brackets omitted). "[A] defendant's placing goods into the stream of commerce 'with the expectation that they will be purchased by consumers within the forum State' may indicate purposeful availment." *J. McIntyre Mach., Ltd. v. Nicastro*, 564 U.S. 873, 881-82 (2011) (quoting *World-Wide Volkswagen Corp. v. Woodson*, 444 U.S. 286, 298 (1980)). However, "[t]he defendant's transmission of goods permits the exercise of jurisdiction only where the defendant can be said to have targeted the forum; as a general rule, it is not enough that the defendant might have predicted that its goods will reach the forum State." *Nicastro*, 564 U.S. at 882. In analyzing specific jurisdiction, the court asks whether the defendant purposefully availed "itself of the privilege of conducting activities within the forum State, thus invoking the benefits and protections of its laws." *Id.*

Plaintiff argues that this court's exercise of specific jurisdiction over Shire Development LLC is appropriate because Shire Development LLC (as the NDA holder for Lialda) placed Lialda into the stream of commerce to reach Alabama consumers, such as

himself. (Doc. # 79 at p. 7). Plaintiff does not dispute that Shire Development LLC has not *in actuality* manufactured, sold, or distributed Lialda. Rather, Plaintiff contends that Shire Development LLC, as the NDA holder, should also be considered a "manufacturer" for the purposes of this jurisdictional inquiry. (Doc. # 82 at p. 4). The court is skeptical of these semantics but, in any event, notes that the word used to describe Shire Development LLC is irrelevant to whether Shire Development LLC "targeted" the State of Alabama and has purposeful availment contacts within the State. *Cf. Nicastro*, 564 U.S. at 882.

Plaintiff advances several theories as to how Shire Development LLC targeted the State of Alabama. None of them have merit. First, Plaintiff claims that Shire Development LLC established sufficient minimum contacts with the State "[w]hen [it] sought permission from the FDA to manufacture, market and sell Lialda® in Alabama (and other states)." (Doc. # 82 at p. 8). But, simply seeking permission from the FDA or submitting an NDA does not rise to the level of targeting Alabama or invoking the benefits and protections of its laws (especially when none of these activities occurred within Alabama or were directed at Alabama). *See Nicastro*, 564 U.S. at 882. Second, Plaintiff argues that Shire Development LLC purposefully availed itself to Alabama by crafting a defective label that it knew would be purchased by Alabama residents and failing to enhance this allegedly defective label. (Doc. # 82 at p. 8). This argument also misses the mark as "it is not enough that the defendant might have predicted that its goods will reach the forum State." *Nicastro*, 564

U.S. at 882. Finally, Plaintiff appears to present an alter ego theory of liability, attributing the actions of the Shire entities that actually sold Lialda to Shire Development LLC. (Docs. # 79 at p. 9 n.13; 82 at p. 8). However, Plaintiff has not included any facts in his pleadings or any proposed added allegations in his briefing to support such a theory. Because Plaintiff has not provided the court with any support for the proposition that Shire Development LLC targeted the State or invoked the benefits and protections of its laws, there is no basis for the court to reinstate Shire Development LLC as a defendant in this action. *See Nicastro*, 564 U.S. at 882.

Defendants also argue that an amended complaint adding Shire Development LLC would be futile because Plaintiff cannot state a claim against Shire Development LLC under the AEMLD (the only remaining claim in this case). (Doc. # 81). The court finds it unnecessary to explore this argument because, as discussed above, Shire Development LLC has had no purposeful availment contacts with the State that support this court's exercise of specific jurisdiction over it in this product liability action. Because reinstating Shire Development LLC would be futile, Plaintiff's Motion to Reinstate (Doc. # 79) is due to be denied.

V. Conclusion

For the reasons stated above, both the Motion to Reinstate (Doc. # 79) and the Motion for Reconsideration (Doc. # 91) are due to be denied. A separate Order will be entered in accordance with this Memorandum Opinion.

DONE and **ORDERED** this May 10, 2018.

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R. DAVID PROCTOR

UNITED STATES
DISTRICT JUDGE

Appendix G

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA

No. 2:16-CV-00963

MARK BLACKBURN,

Plaintiff,

v.

SHIRE U.S., INC., et al.,

Defendants.

Filed: Nov. 2, 2017

MEMORANDUM OPINION

This matter is before the court on Plaintiff/Movant's Motion to Alter or Amend Order and Motion to Amend Complaint. (Doc. # 64). The Motion (Doc. # 64) has been fully briefed. (Docs. # 64, 65, 73, 74). For the reasons explained below, the Motion (Doc. # 64) is due to be denied.

I. Background

Defendants engage in the distribution, marketing, and sale of the drug known as Lialda. (Doc. # 41 at ¶ 8). In November 2013, Plaintiff was prescribed Lialda for treatment of his Crohn's disease. (*Id.* at ¶ 39). Plaintiff took Lialda, as prescribed, from November 2013 until February 2015. (*Id.*). In

September 2015, Plaintiff was diagnosed with Stage IV renal failure and severe chronic interstitial nephritis. (*Id.* at ¶ 45). On June 10, 2016, Plaintiff filed a complaint against Shire US Inc., Shire LLC, Shire Development LLC, Shire Pharmaceutical Development, Inc., and Shire Pharmaceuticals LLC. (Doc. # 1).

On October 5, 2016, Defendants moved to dismiss Plaintiff's claims. (Docs. # 26, 27). Plaintiff filed an opposed motion to amend his complaint on October 24, 2016, and the court granted Plaintiff leave to amend on November 1, 2016. (Docs. # 36, 40). On November 2, 2016, Plaintiff filed a First Amended Complaint. (Doc. # 41). In his First Amended Complaint, Plaintiff asserted that Defendants' recommendation of only "periodic" renal testing while using Lialda, as opposed to the more specific testing regimen detailed in his Amended Complaint, proximately caused his kidney injury. (*Id.* # 41 at ¶ 26). Specifically, Plaintiff asserted claims for failure to warn under the Alabama Extended Manufacturers Liability Doctrine ("AEMLD") (Count One), fraud (Count Two), suppression and concealment (Count Three), and breach of express warranty (Count Four). (Doc. # 41).

On November 16, 2016, Defendants moved to dismiss Plaintiff's First Amended Complaint. (Docs. # 44, 45). On May 8, 2017, the court dismissed Counts Two, Three, and Four with prejudice and denied Defendants' motion to dismiss Count One without prejudice. (Docs. # 53, 54). After granting Defendants' motion to dismiss for lack of personal jurisdiction on May 12, 2017, the court dismissed Defendants Shire Development LLC, Shire Pharmaceutical

Development, Inc., and Shire Pharmaceuticals LLC without prejudice. (Doc. # 56). On June 29, 2017, Plaintiff filed a Motion to Alter or Amend Order and Motion to Amend Complaint (Doc. # 64), which is discussed in turn.

II. Analysis

Plaintiff has asked the court to amend its Order (Doc. # 54) dismissing with prejudice Counts Two, Three, and Four of Plaintiff's First Amended Complaint (Doc. # 41). (Docs. # 64, 65). Specifically, Plaintiff asks the court to enter a revised order dismissing these counts without prejudice and to grant Plaintiff leave to amend his complaint a second time. (*Id.*). Plaintiff erroneously argues that he is entitled to an opportunity to cure the deficiencies in his First Amended Complaint (Doc. # 41). (Doc. # 65 at p. 3-5).

In cases where a plaintiff has acted in good faith and has not been given an initial chance to amend its complaint, dismissal with prejudice is a remedy of last resort. *Eiber Radiology, Inc. v. Toshiba Am. Med. Sys., Inc.*, 673 F. App'x 925, 929 (11th Cir. 2016); *cf.* Fed. R. Civ. Pro. 15(a)(2) ("The court should freely give leave [to amend] when justice so requires."). When a more carefully drafted complaint might state a claim, a district court should grant a *pro se* plaintiff at least one chance to amend its complaint before dismissing the action with prejudice; however, such leniency is not required when a plaintiff has been represented by counsel. *Eiber Radiology*, 673 F. App'x at 929; *see Wagner v. Daewoo Heavy Indus. Am. Corp.*, 314 F.3d 541, 542 (11th Cir. 2002) (partially overruling *Bank v. Pitt*, 928 F.2d 1108, 1112 (11th Cir. 1991), by ruling

that a district court is not required to grant a counseled plaintiff leave to amend his complaint *sue sponte*). The Eleventh Circuit has "never required district courts to grant counseled plaintiffs more than one opportunity to amend a deficient complaint, nor [has the Eleventh Circuit] concluded that dismissal with prejudice is inappropriate where a counseled plaintiff has failed to cure a deficient pleading after having been offered ample opportunity to do so." *Eiber Radiology*, 673 F. App'x at 930; *see Henley v. Turner Broad. Sys., Inc.*, __ F. Supp. 3d __, 2017 WL 3158142, at *16 (N.D. Ga. July 25, 2017) ("The Court also concludes it is unnecessary to allow Plaintiffs, who are represented by counsel, the opportunity to file a further amended complaint.").

In this case, Plaintiff had ample opportunity to state claims on which relief could be granted. *See Eiber Radiology*, 673 F. App'x at 930 (affirming a district court's dismissal of an amended complaint with prejudice). After Defendants initially moved to dismiss Plaintiff's complaint (Doc. # 26), the court granted Plaintiff leave to amend his complaint. (Doc. # 40). Once Plaintiff filed his First Amended Complaint (Doc. # 41), Defendants again moved to dismiss the case. (Doc. # 44). Rather than requesting leave to amend his complaint a second time *before* the court ruled on this motion to dismiss, Plaintiff sat "idly by as he awaited the district court's determination" of Defendants' second motion to dismiss. *Wagner*, 314 F.3d at 543. Allowing Plaintiff "a second bite at [the]

apple"[1] not only would be prejudicial to Defendants but also would be contrary to promoting judicial efficiency. *See Eiber Radiology*, 673 F. App'x at 930. Accordingly, it is unnecessary to allow Plaintiff the opportunity to file a second amended complaint, and this Motion (Doc. # 64) is due to be denied.

III. Conclusion

For the reasons explained above, Plaintiff's Motion to Alter or Amend Order and Motion to Amend Complaint (Doc. # 64) are denied. An order consistent with this Memorandum Opinion will be entered.

DONE and **ORDERED** this November 2, 2017.

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R. DAVID PROCTOR

UNITED STATES
DISTRICT JUDGE

[1] In reality, this would be Plaintiff's *third* bite at the apple. Plaintiff has already filed an initial complaint (Doc. #1) and has been given the opportunity to amend that complaint (Doc. #41).

Appendix H

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA

No. 2:16-CV-00963

MARK BLACKBURN,

Plaintiff,

v.

SHIRE U.S., INC., et al.,

Defendants.

Filed: May 8, 2017

MEMORANDUM OPINION

I. Introduction

This matter is before the court on Defendants' Motion to Dismiss Plaintiff's First Amended Complaint. (Doc. # 44). In their motion and accompanying memorandum of law (Doc. # 45), Defendants argue that Plaintiff's Amended Complaint is due to be dismissed in its entirety. Defendants' motion is fully briefed. (Docs. # 45, 51, 52). For the reasons stated below, Defendants' Motion is due to be granted in part and denied in part.

II. Factual Background[1]

Defendants engage in the distribution, marketing, and sale of the drug known as LIALDA. (Doc. # 41 at ¶ 8). In November 2013, Plaintiff was prescribed LIALDA for treatment of his Crohn's disease. (*Id.* at ¶ 39). Plaintiff took LIALDA, as prescribed, from November 2013 until February 2015. (*Id.*). In September 2015, Plaintiff was diagnosed with Stage IV renal failure and severe chronic interstitial nephritis. (*Id.* at ¶ 45). Plaintiff contends that LIALDA causes toxicity to build up in the kidneys over time, and he alleges that his kidney injuries were a direct result of his continued use of LIALDA. (*Id.* at ¶¶ 43-47).

Plaintiff asserts that LIALDA's label contained a defect, which was present both in January 2007 (when LIALDA was initially approved by the FDA), and in November 2013 (when Plaintiff was first prescribed LIALDA). (*Id.* at ¶¶ 17, 18). He contends that LIALDA's defective label caused his injuries. (*Id.* at ¶¶ 36, 47). LIALDA's label warned of the possibility that a consumer may develop kidney damage from use of the product. Indeed, the LIALDA label in use at the time Plaintiff was prescribed the drug[2] warned that "[r]enal impairment, including minimal change nephropathy, acute and *chronic interstitial nephritis*,

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[1] For purposes of evaluating Defendants' Motion to Dismiss, the court assumes the veracity of Plaintiff's well-pleaded factual allegations. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009).

[2] Plaintiff quotes language from both LIALDA's 2007 and 2013 labels, but asserts that, with respect to the language made the basis of his complaint, the two are "substantively identical." (Doc. #41 at ¶ 19).

and rarely, *renal failure*, has been reported in patients given products such as LIALDA that contain mesalamine or are converted to mesalamine." (*Id.* at ¶ 18) (emphasis added). Accordingly, Plaintiff does not contend that Defendants failed to warn that use of LIALDA may result in kidney injury.

Instead, he takes issue with the following language, also from LIALDA's label: "[i]t is recommended that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy." (*Id.*). Plaintiff alleges that this recommended "periodic" evaluation constitutes a defective and unsafe instruction for use of LIALDA. (*Id.* at ¶ 22). He contends that the term "periodic," as generally used in drug labels, refers to either semi-annual or annual testing. (*Id.*). However, he asserts that an appropriate LIALDA label should include instructions recommending "evaluation of renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year." (*Id.* at ¶ 25). Plaintiff asserts that Defendants' recommendation of only "periodic" testing, as opposed to the more specific testing regimen detailed in his Amended Complaint, proximately caused his kidney injury. (*Id.* at ¶ 26). Plaintiff asserts claims for failure to warn under the Alabama Extended Manufacturers Liability Doctrine ("AEMLD"), fraud, suppression and concealment, and breach of express warranty.

III. Standard of Review

The Federal Rules of Civil Procedure require only that the complaint provide "a short and plain

statement of the claim showing that the pleader is entitled to relief." Fed. R. Civ. P. 8(a)(2). Still, the complaint must include enough facts "to raise a right to relief above the speculative level." *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544, 555 (2007). Pleadings that contain nothing more than "a formulaic recitation of the elements of a cause of action" do not meet Rule 8 standards, nor do pleadings suffice that are based merely upon "labels and conclusions" or "naked assertion[s]" without supporting factual allegations. *Twombly*, 550 U.S. at 555, 557. In deciding a Rule 12(b)(6) motion to dismiss, courts view the allegations in the complaint in the light most favorable to the nonmoving party. *Watts v. Fla. Int'l Univ.*, 495 F.3d 1289, 1295 (11th Cir. 2007).

To survive a motion to dismiss, a complaint must "state a claim to relief that is plausible on its face." *Twombly*, 550 U.S. at 570. "A claim has facial plausibility when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). Although "[t]he plausibility standard is not akin to a 'probability requirement,'" the complaint must demonstrate "more than a sheer possibility that a defendant has acted unlawfully." *Id*. A plausible claim for relief requires "enough fact[s] to raise a reasonable expectation that discovery will reveal evidence" to support the claim. *Twombly*, 550 U.S. at 556. The Supreme Court has recently identified "two working principles" for a district court to use in applying the facial plausibility standard. First, in evaluating motions to dismiss, the court must assume the veracity of well-pleaded factual allegations; however,

the court does not have to accept as true legal conclusions when they are "couched as ... factual allegation[s]." *Iqbal*, 556 U.S. at 678. Second, "only a complaint that states a plausible claim for relief survives a motion to dismiss." *Id.* at 679.

Application of the facial plausibility standard involves two steps. Under prong one, the court must determine the scope and nature of the factual allegations that are well-pleaded and assume their veracity; and under prong two, the court must proceed to determine the claim's plausibility given the well-pleaded facts. That task is context specific and, to survive the motion, the allegations must permit the court based on its "judicial experience and common sense ... to infer more than the mere possibility of misconduct." *Id.* If the court determines that well-pleaded facts, accepted as true, do not state a claim that is plausible, the claims are due to be dismissed. *Id.*

IV. IV. Analysis

Defendants' brief in support of their Motion to Dismiss makes a number of arguments which purport to establish bases to dismiss Plaintiff's Amended Complaint. The court will address Defendants' arguments in turn.

A. Impossibility Preemption

It is axiomatic that "[u]nder the Supremacy Clause, state laws that require a private party to violate federal law are pre-empted and, thus, are 'without effect.'" *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2470 (2013) (quoting *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981)). However, "[i]n all pre-emption cases, and particularly in those in which

Congress has 'legislated… in a field which the States have traditionally occupied,' … we 'start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'" *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)). Here, Defendants argue that Plaintiff's state law claims, which allege that LIALDA's label is inadequate under state law, are preempted by federal law related to the labelling of prescription drugs. (Doc. # 45 at pp. 13-18).

While Plaintiff alleges that Defendants had a duty under Alabama state law to issue adequate testing requirements and warnings (*see* Doc. # 41 at ¶ 150), federal law imposes more complex drug labeling requirements. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612 (2011). Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), drug manufacturers must gain approval from the United States Food and Drug Administration ("FDA") before marketing any drug in interstate commerce. *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2470 (2013); *see* 21 U.S.C. § 355(a). This premarket approval of a new drug application ("NDA") requires FDA approval of the exact text contained in the drug's proposed label. *See* 21 U.S.C. § 355; 21 C.F.R. §314.105(b). The FDA may approve of an NDA only if the drug in question is "safe for use" under "the conditions of use prescribed, recommended, or suggested in the proposed labelling thereof." 21 U.S.C. § 355(d).

Generally, "a manufacturer may only change a drug label after the FDA approves a supplemental

application." *Wyeth v. Levine*, 555 U.S. 555, 568 (2009); 21 C.F.R. § 314.70. However, there are certain instances in which a drug manufacturer may unilaterally make changes to a drug's label without the FDA's prior approval. Under the "changes being effected" ("CBE") regulation, a manufacturer may unilaterally change the label of its drug to "add or strengthen a contraindication, warning, precaution, or adverse reaction" without waiting for FDA approval. § 314.70(c)(6)(iii)(A).

In those instances when state and federal law conflict, and it is "impossible for a private party to comply with both state and federal requirements," state law is preempted. *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995) (internal quotation marks omitted). Given their obligations under the FDCA, Defendants argue that it would be impossible for them to comply with federal labelling requirements as well as the state duty Plaintiff contends LIALDA's label breached. The court disagrees.

In circumstances such as those presented here, "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc.*, 564 U.S. at 620. And, in a case involving facts similar to those here, the Supreme Court found that a plaintiff's state law claims were not preempted by federal labelling requirements. *Wyeth*, 555 U.S. at 573. In *Wyeth*, the plaintiff filed suit against a brand name drug manufacturer claiming that a drug that it manufactured did not contain an adequate warning. *Id.* at 565. In conducting its "impossibility" analysis, the Court noted that the CBE regulation permitted

the defendant to strengthen its drug's warning before receiving the FDA's approval. *Id.* at 571. Because the defendant could "unilaterally strengthen its warning… the mere fact that the FDA approved [the drug in question's] label does not establish that it would have prohibited such a change." *Id.* at 573.

The same is true here. Defendants note that an NDA holder may only utilize the CBE supplement process when "newly acquired information" becomes available which would support the change sought to be made. (Doc. # 45 at p. 19 (citing *In re: Celexa and Lexapro Marketing and Sales Practices Litigation*, 779 F.3d 34, 37 (1st Cir. 2015); 21 C.F.R. § 314.70(c)(6)). However, in his Amended Complaint, Plaintiff has alleged the existence of "newly acquired information."

> Newly acquired information is data, analyses, or other information not previously submitted to the [FDA], which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 314.3. In *Wyeth*, the Court rejected a "cramped reading of the CBE regulation" and noted that "newly acquired information" is not limited to new data, but includes new analyses of previously submitted data. *Wyeth*, 555 U.S. at 569, 570.

Here, Plaintiff has plausibly pled the existence of "newly acquired information" which could warrant the use of the CBE supplementation process. Plaintiff's

Amended Complaint extensively pleads the existence of (1) recently reported information regarding potential adverse health effects of LIALDA, and (2) recommendations of specific testing regimens similar to the one described in Plaintiff's Amended Complaint. (*See* Doc. # 41 at ¶¶ 29-35, 74-78, 79-82, 83-88, 89-96, 97-115, 120). While Plaintiff notes that evidence of the renal toxicity of LIALDA and his proposed testing regimen existed prior to LIALDA's FDA approval, he alleges that the post-2007 literature and adverse event reports (AERs) (*Id.* at ¶¶ 83-88, 97-115) constitute "newly acquired information" which would have permitted Defendants to change LIALDA's label to recommend his proposed testing regimen. And indeed, at least one article has been published between the initial approval of LIALDA and November 2013 (when Plaintiff was prescribed LIALDA) which specifically proposed the testing regimen which Plaintiff alleges should have been added to LIALDA's label. (*Id.* at ¶ 86). Moreover, approximately fifty additional articles addressing the renal toxicity of mesalamine (the active ingredient in LIADLA) have been published after LIALDA's initial approval and prior to November 2013. (*Id.* at ¶ 88).

And, since LIALDA's initial approval, more than one thousand AERs have been compiled relating to individuals who took LIALDA and later reported a renal disorder. (*Id.* at ¶ 109). Plaintiff's allegations regarding this expanding body of information detailing LIALDA's potential to adversely affect users' kidneys, coupled with his allegations about additional research suggesting the benefits of a testing regimen consistent with the one Plaintiff proposes, plausibly

plead the existence of evidence which could qualify as "newly acquired information" for FDCA purposes.

That evidence of LIALDA's potential renal toxicity existed prior to its approval in 2007 does not alter this conclusion.[3] Plaintiff readily pleads that evidence of LIALDA's renal toxicity, as well as his proposed testing regimen, existed prior to LIALDA's approval. (Doc. # 41 at ¶¶ 59-78). He also pleads, however, that the growing body of evidence relating to LIALDA's potential renal toxicity and his proposed testing regimen constitutes newly acquired information sufficient to support use of the CBE process. (Doc. # 41 at ¶ 139). Newly acquired information is not limited to data which is submitted to (or available to) the FDA for the first time—it also includes new analyses of previously existing data. 21 C.F.R. § 314.3; *Wyeth*, 555 U.S. at 569, 570. Indeed, such evidence can have a cumulative effect, and the continued increase of AERS and/or medical literature can constitute "newly acquired information." *See Newman v. McNeil Consumer Healthcare*, 2012 WL 39793, at *10 (N.D. Ill. Jan. 9, 2012) (finding that

[3] In addition to the specific articles Plaintiff specifically mentions in his Amended Complaint, he has attached a list of medical articles relating to the nephrotoxicity of mesalamine as an exhibit to his complaint. (Doc. # 41-5). The court may consider this exhibit in ruling on Defendants' motion to dismiss. *Page v. Postmaster Gen. and Chief Exec. Officer of the U.S. Postal Serv.*, 493 Fed. Appx. 994, 995 (11th Cir. 2012). ("[E]xhibits attached to the complaint are treated as part of the complaint for Rule 12(b)(6) purposes" and may be considered without converting a motion to dismiss into a motion for summary judgment). Many of the articles included in this list were published prior to LIALDA's approval in 2007.

AERs reported after 2005 could constitute new information that might change the FDA's analysis, where the FDA had considered the existence of AERs prior to 2005 and rejected their significance). Such is the case here. While evidence of LIALDA's possible renal toxicity and Plaintiff's proposed testing regimen certainly existed prior to LIALDA's approval, Plaintiff has plausibly pled facts which would show that evidence supporting his proposed testing regimen increased following the FDA's approval of LIALDA. Assuming the facts pled in Plaintiff's amended complaint to be true, as the court must under these circumstances, this expansion of research and evidence regarding the need for, and efficacy of, Plaintiff's proposed testing regimen allegations plausibly indicates the existence of newly acquired information which was available and counseled in favor of a change to the renal testing recommendation included on LIALDA's label.

Because of this newly acquired information, Plaintiff has properly alleged that Defendants were unilaterally able to change their label pursuant to the CBE supplementation process. Accordingly, there can be no impossibility preemption here "[a]bsent clear evidence that the FDA would not have approved a change." *Wyeth*, 555 U.S. at 571.

1. At This Stage, Defendants Have Not Shown "Clear Evidence" That The FDA Would Not Have Approved Plaintiff's Proposed Change

Defendants argue that even if they could have made changes to LIALDA's label pursuant to the CBE process (which they do not concede was possible), the

FDA still would not have approved of Plaintiff's proposed label change. (Doc. # 45 at p. 15). Specifically, Defendants argue that the label change which Plaintiff proposes would require Defendants to change not only the "Full Prescribing Information" section of LIALDA's label, but also the "Highlights" section of the drug label.

The "clear evidence" standard is a difficult one to meet at the pleadings stage. Here, Defendants must show, on the Plaintiff's pleadings alone, that the FDA would not have approved the change which Plaintiff has suggested. *Wyeth*, 555 U.S. at 571. However, as is the case here, plaintiffs rarely plead the existence of facts which would undermine their case in that fashion. With the benefit of Rule 56 evidence, courts have found preemption based on "clear evidence" provided by a defendant. *See Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264 (W.D. Okla. 2011) (finding preemption of a plaintiff's failure to warn claim where the defendant provided undisputed evidence that the express type of warning the plaintiff claimed the manufacturer should have included had been previously considered and rejected by the FDA). However, while such evidence may exist in this case, it is not before the court on Defendants' present motion. Accordingly, Defendants argue here that the FDA regulations themselves, read in conjunction with the facts in Plaintiff's Amended Complaint, demonstrate that the FDA would not have approved Plaintiff's proposed label change.

As discussed above, the CBE regulation allows a drug manufacturer to change its label upon filing its supplemental application with the FDA; it need not

wait for FDA approval. 21 C.F.R. § 314.70(c)(6); *Wyeth v. Levine*, 555 U.S. at 568. However, in almost all instances, any change to the Highlights section of an approved drug's label requires FDA approval. *See* 21 C.F.R. § 314.70(b)(2)(v)(C) (categorizing any change to the information required by § 201.57(a)—the section detailing the specific requirements of the Highlights section—as a "major change" which requires FDA approval before it can be made). Again, in circumstances such as these, a private party's claim is only preempted if the drug manufacturer was not able to act independently under federal law to do what state law requires. That is, preemption exists "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance." *PLIVA, Inc.,* 564 U.S. at 623-24. Such assistance "is dependent on the exercise of judgment by a federal agency," and as such "that party cannot independently satisfy those state duties for preemption purposes." *Id.* at 624. Accordingly, when sufficient newly acquired information exists in order to support a label change under the CBE process, as has been plausibly pled here, the claim is not preempted.

However, the same cannot be said with respect to Plaintiff's assertion that a change to the Highlights section would be permitted here. Where a private party seeks a label change which requires FDA approval, such as a change to the Highlights section, impossibility preemption exists. Plaintiff argues that even if his proposed change necessitated a change to the Highlights section, it would still not risk conflict preemption. (Doc. # 51 at p. 21). He argues that such a change would not be "impossible," because

Defendants could have sought expedited FDA approval of the Highlights section change or asked the FDA to waive such an approval requirement by submitting a written waiver request to the FDA. (*Id.*). The court disagrees. This is precisely the sort of argument that the *PLIVA, Inc.* court rejected. *PLIVA, Inc.*, 564 U.S. at 623-24. The "impossibility" inquiry turns on a private party's ability to act independently. It is of no consequence that the FDA may have allowed a change to the Highlights section of LIALDA. Because Defendants could not have independently changed the Highlights section of LIALDA in order to conform to state law, any argument that begins with the theory that Defendants could (or should) have changed the Highlights section of LIALDA's label ends in preemption.

The balance of Plaintiff's claims are premised on the contention that LIALDA's label should recommend a specific kidney testing regimen, rather than recommend only "periodic" testing. And LIALDA's recommendation of "periodic" testing occurs both in the Full Prescribing Information and Highlights section of its label. The Highlights section of LIALDA's label notes: "[r]enal impairment may occur. Assess renal function at the beginning of treatment and *periodically during treatment*." (Doc. # 41-2 at p. 2) (emphasis added). The label then refers the reader to Section 5.1 of the Full Prescribing Information ("FPI") under "Warnings and Precautions," which includes a more detailed warning and again recommends testing of renal function "periodically." (*Id.* at p. 2, 3). To the extent that Plaintiff's Amended Complaint seeks relief for an alleged defect in the FPI warning, there is no

preemption at this stage of litigation, because Plaintiff has plausibly pled that Defendants could have utilized the CBE process.

However, LIALDA's label also recommends "periodic" testing in its Highlights section. (Doc. # 45 at p. 21). Because Plaintiff alleges that this recommendation is deficient under state law, Defendants contend that Plaintiff's Amended Complaint seeks relief which requires a change to the Highlights section of LIALDA's label, and as such is preempted pursuant to FDA regulations. (*Id.*). Plaintiff's retort, while perhaps tenuous, is sufficient at this stage to overcome Defendants' motion to dismiss. Plaintiff argues that the language in the Highlights section of a drug's label is not required to mirror the language found in the FPI section of that label. (Doc. # 51 at p. 19).[4] Accordingly, he argues that had Defendants changed the LIALDA Label in the "below the line" Prescribing Information to define 'periodically' to include his proposed testing regimen, no 'major change' to the Highlights section would have been required." (Doc. # 51 at p. 20). Essentially, he contends that if the term "periodically" were changed in the FPI section to reflect his proposed testing regimen, it would be no more than "a mere clarification or fleshing out of the term 'periodically,'" and would not require a change of the term

[4] For support of his position, Plaintiff notes that certain required language included in every Highlights section—"[t]hese highlights do not include all the information needed to use [LIALDA] safely and effectively"—effectively demonstrates that changes made to the FPI section of a drug label need not always be reflected in the Highlights section as well. (Doc. # 51 at pp. 19-20 (citing 21 C.F.R. § 201.57(a)(1)).

"periodically" in the Highlights section of LIALDA's label. (*Id.* at n. 29). As such, his amended complaint alleges that Defendants could have changed the recommendation for "periodic" testing in the FPI section of LIALDA's label, but left recommendation for "periodic" testing in the Highlights section.

To be sure, this theory may place Plaintiff on shaky ground going forward. On the one hand, Plaintiff alleges that LIALDA's recommendation that users undergo "periodic" renal testing was deficient to the point of violating state law. But on the other, he contends that his proposed recommended renal testing is no more than a clarification of the term "periodic" referenced in LIALDA's Highlights section. Defendants argue that this is an inconsistency which bars his claim on either state law or preemption grounds. (Doc. # 52 at p. 6, n.4). However, Plaintiff has plausibly, if just barely, pled a set of circumstances which survives both the state law and preemption hurdles raised in Defendants' motion to dismiss. Plaintiff's Amended Complaint specifically quotes from the FPI section of LIALDA's label (as opposed to the Highlights section), and states that the term "periodic" is defective because it typically connotes semi-annual or annual testing. (Doc. # 41 at ¶¶ 17-18, 22-23). And when detailing the factual basis for his AEMLD claim, Plaintiff again referenced only the language contained in the FPI section warning, and did not plead that the warning in the Highlights section was also defective. (*Id.* at ¶¶ 157-58). Plaintiff's AEMLD claim, then, is one brought on the basis of an alleged half-truth. Plaintiff does not allege that Defendants failed to warn of LIALDA's possible renal toxicity, or failed to recommend a renal testing

regimen for LIALDA users. Rather, Plaintiff bases his AEMLD claim on the contention that the renal testing recommendation contained in the FPI section of LIALDA's label is inadequate. This allegation, at the motion to dismiss stage, is sufficient to satisfy Plaintiff's pleading requirements on both state law and preemption grounds.

B. The Learned Intermediary Doctrine Does Not Bar Plaintiff's Claims

Defendants next argue that Plaintiff's claims are barred by the learned intermediary doctrine. (Doc. # 45 at p. 24). "Alabama's learned intermediary doctrine imposes on a prescription drug company a duty to provide warnings *solely* to the prescribing physician rather than to the patient directly." *Allain*, 2015 WL3948961, at *8 (citing *Stone v. Smith, Kline & French Labs.*, 447 So. 2d 1301, 1304 (Ala. 1984)) (additional citations omitted). The Alabama Supreme Court has stated that:

> [t]he principle behind the learned-intermediary doctrine is that prescribing physicians act as learned intermediaries between a manufacturer of a drug and the consumer/patient and that, therefore, the physician stands in the best position to evaluate a patient's needs and to assess the risks and benefits of a particular course of treatment for the patient.

Wyeth, Inc. v. Weeks, 159 So. 3d 649, 672-73 (Ala. 2014). This doctrine exists because consumers can obtain prescription drugs only through a physician or other qualified healthcare provider, and physicians are trained to understand the highly technical

warnings required by the FDA in drug labeling. *Id.* at 673 (citing 21 U.S.C. § 353(b)(1); 21 C.F.R. § 201.56). The doctrine "recognizes the role of the physician as a learned intermediary between a drug manufacturer and a patient." *Id.*

"Under the learned intermediary doctrine the adequacy of [Defendant's] warning is measured by its effect on the physician, to whom it owe[s] a duty to warn, and not by its effect on the consumer." *Weeks*, 159 So. 3d at 673 (quoting *Toole v. Baxter Healthcare Corp.*, 235 F.3d 1307, 1313-14 (11th Cir. 2000)) (citations, quotations and changes omitted). "A prescription-drug manufacturer fulfills its duty to warn the ultimate users of the risks of its product by providing adequate warnings to the learned intermediaries who prescribe the drug. Once that duty is fulfilled, the manufacturer has no further duty to warn the patient directly." *Id.* To be sure, "[h]owever, if the warning to the learned intermediary is inadequate or misrepresents the risk, the manufacturer remains liable for the injuries sustained by the patient." *Id.* But, for this to be the case, a patient must make a specific showing: "that the manufacturer failed to warn the physician of a risk not otherwise known to the physician and that the failure to warn was the actual and proximate cause of the patient's injury." *Id.* at 673-74.

Defendants argue that Plaintiff has not plausibly alleged facts indicating that Defendants failed to adequately warn his physician, Dr. Ferrante, of the dangers of LIALDA. Specifically, Defendants contend that Plaintiff has failed to properly plead any plausible facts that show: (1) Defendants failed to

adequately warn Dr. Ferrante of the dangers of LIALDA; (2) Dr. Ferrante did not understand or appreciate LIALDA's warning; (3) Defendants failed to warn Dr. Ferrante of a risk "not otherwise known" to him; and (4) the alleged defect in LIALDA's label was the actual and proximate cause of his injury. The court disagrees.

Plaintiff's Amended Complaint pleads a number of facts which, taken as true, plausibly make out an AEMLD claim which survives Defendants' "learned intermediary" defense. Plaintiff pled that the term "periodic," as used in Defendants' LIALDA label, is generally used in drug labels to mean either semi-annual or annual testing. (Doc. # 41 at ¶ 22). Moreover, he pled that many physicians interpret and understand recommendations for "periodic" testing to mean testing at the patient's next physical examination, which could be a year or more after initiation of LIALDA's therapy. (*Id.* at ¶ 23). Plaintiff alleges that Dr. Ferrante is a gastroenterologist, and that the mesalamine-related medical literature and AERs which may have alerted him to Plaintiff's proposed testing regimen actually related to the field of nephrology, one with which he has no special knowledge. (*Id.* at ¶¶ 56-58).

Plaintiff has specifically pled that LIALDA's warning was inadequate, and that Dr. Ferrante reasonably relied on LIALDA's defective warning. (*Id.* at ¶¶ 155-60, 169). And, he has pled specific facts which bypass the learned intermediary doctrine. Plaintiff's Amended Complaint pleads that professionals such as Dr. Ferrante commonly assign a meaning to "periodic" which is different than the

testing regimen he asserts is efficacious. (*Id.* at ¶¶ 22-23). As such, Plaintiff has plausibly pled that Defendants failed to adequately warn Dr. Ferrante, and that Dr. Ferrante did not fully appreciate LIALDA's warning. Moreover, by distinguishing the fields of gastroenterology and nephrology, Plaintiff has, at least at this stage, plausibly pled that LIALDA's label, which did not include specific details regarding the implementation of a testing regimen in its recommendation, failed to warn Dr. Ferrante of a risk not otherwise known to him.

Defendants' contention that Plaintiff's claims fail for lack of proximate cause is similarly off the mark. Defendants argue that Plaintiff has not alleged that a different warning would have altered Dr. Ferrante's decision to prescribe LIALDA to Plaintiff, and as such, Plaintiff has not pled that LIALDA's allegedly defective label caused his injury. (Doc. # 45 at p. 27). This is a typical way of assessing the proximate cause inquiry. *Weeks*, 159 So. 3d at 673-74. However, it is not the only way. 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. *Barnhill v. Teva Pharm, USA, Inc.*, 819 F. Supp. 2d 1254, 1261 (S.D. Ala. 2011); *Fields v. Eli Lilly & Co.*, 116 F. Supp. 3d 1295, 1307 (M.D. Ala. 2015). Here, Plaintiff has not alleged that Dr. Ferrante would not have prescribed him LIALDA if the drug's label had been adequate. Instead, Plaintiff acknowledges that LIALDA's label warns of the risk of kidney damage, but contends that an adequate label would have recommended a specific

method by which LIALDA users should test to determine whether they had developed kidney damage. (Doc. # 45 at ¶ 167). Here, Plaintiff has plausibly pled the existence of proximate cause. He has pled sufficient facts which purport to establish that if LIALDA's label were adequate, Dr. Ferrante would have recommended a specific renal testing regimen, which Plaintiff would have followed, which, in turn, would have detected potential impairment of his kidney function in the early stages of its development. (Doc. # 41 at ¶¶ 161-165). Accordingly, because Count One (AEMLD) of Plaintiff's Amended Complaint is neither preempted by federal law nor barred by the learned intermediary doctrine, Defendants' motion to dismiss is due to be denied to the extent that it seeks dismissal of that count.

C. Plaintiff's Breach of Express Warranty Claim is Due to be Dismissed

In Count Four of his Amended Complaint, Plaintiff advances a claim for breach of express warranty. (Doc. # 41 at ¶ 210). Plaintiff alleges that LIALDA's label "constituted a warranty that compliance with [its recommended testing] would make use of the LIALDA product safe." (*Id.* at ¶ 215). However, he contends that LIALDA failed to conform to this express warranty because use of LIALDA in conformity with its warning label (which recommends only "periodic" testing) was unsafe. (*Id.* at ¶ 216). Defendants counter this assertion in their motion to dismiss, and argue that the language in the LIALDA label cannot be construed to represent an "express warranty of safeness," and as such Count Four of

Plaintiff's amended complaint is due to be dismissed. (Doc. # 45 at p. 28). The court agrees.

In Alabama, "[a]ny description of the goods which is made part of the basis of the bargain creates an express warranty that the goods shall conform to the description." Ala. Code §7-2-313(1)(b); *see also* Ala. Code §7-2-313(2) (noting that it is not necessary that the seller use formal words such as "warrant" or "guarantee" in order to create an express warranty). However, LIALDA's label simply does not embody any form of express warranty which Defendants have breached. LIALDA's label at the time it was prescribed to Plaintiff (which is attached to Plaintiff's amended complaint) lists a host of warnings and potential adverse consequences associated with the drug. (*See* Doc. # 41-2 at p. 2 (noting the potential that LIALDA users may experience mesalamine-induced acute intolerance syndrome, masalamine-induced cardiac hypersensitivity, hepatic failure, and GI tract obstruction, among other potentially adverse reactions)). LIALDA's label specifically notes that the drug may cause renal impairment in both the Highlights section and FPI section of its label. (*Id.* at pp. 2, 3).

Even to the extent that LIALDA's label can be construed as a "description of goods" which creates an express warranty, that description cannot to be construed as an express warranty of safeness. To the contrary, LIALDA's label represents that it is intended to be used to treat ulcerative colitis, and that its use may cause a number of side effects, including renal impairment or failure. Plaintiff has failed to plead any breach of this purported warranty. Instead,

Plaintiff's amended complaint pleads that he was prescribed LIALDA, he developed certain kidney ailments (of which LIALDA's label warned), and if LIALDA had utilized a different label his kidney ailments would have been discovered sooner. As addressed above, this set of facts plausibly pleads a failure to warn claim under the AEMLD. But, it does not plausibly plead a claim for a breach of express warranty. Accordingly, Defendants' motion to dismiss is due to be granted as to Count Four of Plaintiff's Amended Complaint, and that count is due to be dismissed.

D. Plaintiff's Fraud-Based Claims are Due to be Dismissed

Plaintiff asserts two fraud-based claims in his amended complaint: Count Two, a claim for fraud, and Count Three, a claim for suppression and concealment. In support of his fraud claim, Plaintiff asserts that "[t]he instructions for use in LIALDA's Label constituted a representation to physicians (and patients) that LIALDA therapy would be safe based upon Recommended Periodic Evaluation." (Doc. # 41 at ¶ 175). However, Plaintiff contends that this representation—specifically, the "Warnings and Precautions" provision in Section 5.1 of LIALDA's label—was false. (*Id.* at ¶ 176). Similarly, in support of his suppression and concealment claim, Plaintiff pleads that LIALDA's label failed to disclose the existence of his proposed testing regimen, and instead only offered the "half-truth" that LIALDA users should undergo "periodic" testing of their kidneys while using the drug. (*Id.* at 199-201).

In order to proceed on his fraud claim Plaintiff must plausibly plead (1) a false representation (2) of a material existing fact (3) relied upon by the plaintiff (4) who was damaged as a proximate result of the misrepresentation. *Coastal Concrete Co. v. Patterson*, 503 So. 2d 824, 826 (Ala. 1987). And to proceed on his fraudulent suppression Plaintiff must plausibly plead the existence of the following elements: "(1) a duty on the part of the defendant to disclose facts; (2) concealment or nondisclosure of material facts by the defendant; (3) inducement of the plaintiff to act; (4) action by the plaintiff to his or her injury." *Lambert v. Mail Handlers Ben. Plan*, 682 So. 2d 61, 63 (Ala. 1996).

Both of Plaintiff's fraud-based claims fail for the same reason—Plaintiff has failed to plead the existence of a *material fact* to support his fraud claims. In order for Plaintiff's fraud and fraudulent suppression claims to proceed, he must plausibly allege that Defendants misrepresented a material fact and concealed a material fact. But Plaintiff's amended complaint alleges only deficiencies with the *recommendation* provided in LIALDA's label. Indeed, if Plaintiff alleged that Defendants misrepresented (or concealed) the existence of certain adverse events or potential side effects of LIALDA, the present analysis would be different. *See Brasher v. Sandoz Pharm. Corp.*, 2001 WL 36403362, at *11 (N.D. Ala. Sept. 21, 2001) (finding that a reasonable juror could have concluded that, in reporting 15 incidents of stroke in their package insert, Defendant fraudulently concealed the other 17 strokes that it knew occurred). These are facts which, when misrepresented or concealed, could form the basis of a fraud claim. Similarly, Plaintiff may have pled viable fraud-based

claims had he alleged that Defendants made a "sales pitch" or other representation regarding the safety of its recommended "periodic" renal testing regimen.[5] *See Brasher*, 2001 WL 36403362, at *10. This type of allegation also could potentially support a fraud claim.

But here, Plaintiff's fraud claims attack only the adequacy of LIALDA's recommendation that its users have their renal function assessed "periodically." And while this allegation does serve as a plausibly pled basis for a failure to warn AEMLD claim, it does not form the basis of a fraud claim. LIALDA's label recommends a certain course of treatment, and Plaintiff has argued that a more detailed "clarification" of that course of treatment should have been used. (Doc. # 51 at p. 20, n. 29). This allegation fails to plead the existence of a material fact which Defendants misrepresented or concealed. Accordingly, to the extent Defendants' motion seeks dismissal of Counts Two and Three of Plaintiff's amended complaint, it is due to be granted, and those counts are due to be dismissed.

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[5] While the court assumes the veracity of the facts contained within Plaintiff's amended complaint, the court is not required to afford "conclusions" or "naked assertion[s]" a presumption of truth when evaluating Defendants' motion to dismiss. *Twombly*, 550 U.S. at 555, 557. Here, Plaintiffs' assertion that LIALDA's label constituted a representation that LIALDA therapy would be safe is just such a conclusion. Moreover, it is a conclusion not supported by the facts in Plaintiff's amended complaint. Plaintiff attached LIALDA's 2013 label to his amended complaint. And, as addressed above, LIALDA's label addresses in detail a wide array of potential side effects that LIALDA users may endure and does not state that a LIALDA user would be free from injury if that user followed the label's recommended testing regimen.

V. Conclusion

For the reasons stated above, Defendants' Motion to Dismiss is due to be granted in part and denied in part. A separate order will be entered in accordance with this opinion.

DONE and **ORDERED** this May 8, 2017.

[handwritten: signature]

R. DAVID PROCTOR

UNITED STATES
DISTRICT JUDGE

Appendix I

RELEVANT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

U.S. Const. art. VI, cl. 2

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

21 U.S.C. §355(b)(1)

(b) Filing application; contents

(1)(A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application--

(i) full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use;

(ii) a full list of the articles used as components of such drug;

(iii) a full statement of the composition of such drug;

(iv) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(v) such samples of such drug and of the articles used as components thereof as the Secretary may require;

(vi) specimens of the labeling proposed to be used for such drug;

(vii) any assessments required under section 355c of this title; and

(viii) the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that--

(I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or

(II) claims a method of using such drug for which approval is sought or has been granted in the application.

(B) If an application is filed under this subsection for a drug, and a patent of the type described in subparagraph (A)(viii) is issued after the filing date but before approval of the application, the applicant shall amend the application to include the patent number and expiration date.

21 U.S.C. §355(d)

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by

subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

21 C.F.R. §201.57(a)

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

(1) Highlights limitation statement. The verbatim statement "These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)."

(2) Drug names, dosage form, route of administration, and controlled substance symbol. The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter.

(3) Initial U.S. approval. The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) Boxed warning. A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change

was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

(7) Dosage and administration. A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) Dosage forms and strengths. A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g.,

10-milligram tablets) and whether the product is scored.

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number

and Web address for voluntary reporting of adverse reactions)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) Drug interactions. A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) Use in specific populations. A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) Patient counseling information statement. The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide)."

(15) Revision date. The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

21 C.F.R. §314.70(b)

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved NDA;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to

syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an NDA that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that NDA.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

21 C.F.R. §314.70(c)

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product,

production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full

explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) 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 NDA may commence distribution of the drug product involved upon receipt by the agency

of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is

intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.