Exhibit 1

[DO NOT PUBLISH]

In the

United States Court of Appeals

For the Eleventh Circuit

No. 20-12258

MARK BLACKBURN,

Plaintiff-Appellant,

versus

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

Defendants-Appellees,

SHIRE DEVELOPMENT, LLC, et al.,

Defendants.

Appeal from the United States District Court
for the Northern District of Alabama
D.C. Docket No. 2:16-cv-00963-MHH

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

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.

Exhibit 2

IN THE UNITED STATES COURT OF APPEALS

FOR THE ELEVENTH CIRCUIT

No. 20-12258-BB

MARK BLACKBURN,

Plaintiff - Appellant,

versus

SHIRE US INC,
SHIRE LLC,

Defendants - Appellees,

SHIRE DEVELOPMENT LLC, et al.,

Defendants.

Appeal from the United States District Court
for the Northern District of Alabama

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

BEFORE: JILL PRYOR, LUCK, and BRASHER, Circuit Judges.

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)

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