UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE SUBOXONE (BUPRENORPHINE/NALOXONE) FILM PRODUCTS LIABILITY LITIGATION	)	Case No. 1:24-md-3092
	)	MDL No. 3092
	)	Judge J. Philip Calabrese
This Document Applies to All Cases	)	

OPINION AND ORDER

In this multi-district litigation, Defendants seek to sequence discovery by proceeding first with discovery related to general causation, limiting case-specific discovery and discovery relating to marketing, promotion, and other issues that generally apply to all cases in this MDL. Plaintiffs oppose this request, claiming it will unnecessarily prolong the MDL, poorly use the resources of the Court and the parties, and present difficult problems drawing lines between discovery relating to general causation and other issues. On June 3, 2024, the Court held oral argument on the dispute. For the reasons that follow, the Court **DENIES** Defendants' motion.

BACKGROUND

At this early point in the MDL, the following overview summarizes the background against which the parties argue their respective positions on Defendants' proposal to frontload discovery and rulings on general causation.

Suboxone, a combination of buprenorphine and naloxone, is prescribed as medication-assisted treatment for opioid use disorder and, as relevant here, is designed to be ingested through oral absorption as a tablet or film. Plaintiffs claim

personal injuries from the use of Suboxone film. Specifically, the complaints point to tooth erosion and loss, dental caries, and other serious and permanent dental problems allegedly resulting from the acidity of buprenorphine.

In 2002, the Food and Drug Administration approved Suboxone in tablet form as an orphan drug. Its orphan drug exclusivity expired on October 8, 2009. In early 2006, Defendants began developing Suboxone as a sublingual film and sought a patent in 2009. In 2010, FDA approved Suboxone film, with an exclusivity period through August 2013. In July 2013, Defendants obtained a patent for Suboxone film. Also in 2013, Defendants pulled Suboxone in its tablet form from the market. Since then, Suboxone has only been available in film form.

On January 12, 2022, FDA issued a drug safety communication "warning that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth." (ECF No. 60-3, PageID #526.) FDA based this report on its survey of the medical literature and 305 adverse event reports of dental problems following buprenorphine use. (*Id.*, PageID #528.) Neither the tablet nor film form of Suboxone contained a warning regarding the risk of dental problems. FDA ordered that a new warning about dental problems be added to the prescribing information and patient medication guide for all medicines containing buprenorphine dissolved in the mouth. No warning was required for other forms of buprenorphine, such as injectables or patches.

Within two weeks, eleven medical associations submitted a joint letter to the FDA's commissioner objecting to the warning. (ECF No. 60-4, PageID #534–39.) This

letter, signed mainly by associations whose members are on the front lines of treating opioid addiction, opined that "it is not possible to conclude a causal relationship between exposure to a medication and dental pain when there is such a small proportion [experiencing dental symptoms] compared to the base rate" of use, especially given the two-year onset period from initial exposure to dental symptoms. (*Id.*, PageID #534–35.) Further, the letter contends that "the mechanism of causation is implausible." (*Id.*, PageID #535.) These medical associations called for FDA to retract its warning to avoid harmful effects, including, among other things, a "false choice for patients: risk severe dental problems or risk grave harm from opioids." (*Id.*, PageID #536.)

STATEMENT OF THE CASE

At the initial status conference in this MDL on March 7, 2024, Defendants raised the issue of frontloading fact and expert discovery on general causation. (ECF No. 46, PageID #434.) About a month later, they formally proposed doing so. (ECF No. 61, PageID #647.) Specifically, they ask to proceed first with document discovery consisting of the relevant investigational new drug applications (INDs) and new drug applications (NDAs) relating to Suboxone tablets and film, the clinical trials relating to these drugs, and pharmacovigilance documents (including MedWatch reports and safety reviews and evaluations). (ECF No. 65-1, PageID #687.) Initially, though it is not clear why, Defendants proposed collecting medical records from Plaintiffs in this phase. (ECF No. 60-1, PageID #522; ECF No. 61, PageID #649.) After the Court's April 16, 2024 status conference, Defendants supplemented their proposal by stating

that they "would be agreeable to a process where the Court randomly selects three to five plaintiffs to be included in the general causation phased discovery." (ECF No. 66, PageID #690–91.)

Plaintiffs oppose bifurcating or phasing discovery. (ECF No. 86.) They argue that Defendants' position assumes that their theory of general causation will ultimately fail. Plaintiffs emphasize that they need not prove general causation at the pleading stage and that years of scientific research support a plausible mechanism for general causation. (*Id.*, PageID #906.) Moreover, Plaintiffs argue that other MDLs routinely deny requests to bifurcate discovery because of its inefficiencies and costs.

ANALYSIS

The Court has broad discretion to "tailor discovery narrowly and to dictate the sequence of discovery." *Crawford-El. v. Britton*, 523 U.S. 574, 598–99 (1998). In an MDL, "discretionary matters going to the phasing, timing, and coordination of the cases, [are when] the power of the MDL court is at its peak." *In re National Prescription Opiate Litig.*, 956 F.3d 838, 845 (6th Cir. 2020) (quoting *In re Korean Air Lines Co.*, 642 F.3d 685, 700 (9th Cir. 2011)).

The parties contest the state of the scientific literature regarding any causal relationship between Suboxone and the injuries complained of and the various ways—legally and scientifically—of establishing causation. But the substance of those debates has little bearing at the moment. Instead, the present dispute involves

decisions about case management and the relative burdens and time associated with discovery, experts, and summary judgment.

I. Proof of General Causation

The Court begins with what Plaintiffs must prove to establish general causation. How Plaintiffs go about proving it, or Defendants oppose and resist that proof, remains to be seen and may take any number of forms. When evaluating evidence on general causation, courts and experts commonly employ the factors attributed to Sir Arthur Bradford Hill as a way "to distinguish a causal connection from a mere association." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3d Cir. 2017); *Milward v. Acuity Specialty Prods. Grp.*, 639 F.3d 11, 17–19 (1st Cir. 2011); *see also* Arthur Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965). These factors that guide epidemiologists and other scientists in making judgments about causation are: (1) the temporal relationship between exposure and onset of symptoms or disease; (2) strength of the association in various contexts; (3) the dose-response relationship; (4) replication of the findings; (5) biological plausibility (coherence with existing knowledge); (6) consideration of alternative explanations; (7) cessation of exposure; (8) specificity of the association; and (9) consistency with other knowledge. Michael D. Green, D. Michal Freedman & Leon Gordis, *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence 597–606 (3d ed. 2011).

In addition, "[i]n assessing causation, researchers first look for alternative explanations for the association, such as bias or confounding factors." *Id.* at 597. Of course, the parties may approach general causation through a discipline other than

epidemiology. But the Hill factors illustrate the considerations and types of evidence that will come into play as the parties address general causation in this MDL.

Based on a review of the record at this early stage of the proceedings, the parties' respective briefs and arguments, and how parties in complex litigation involving pharmaceuticals or other exposures that allegedly cause personal injuries typically seek to prove or defeat causation, the Court finds that reliable opinions on general causation will likely be sufficiently bound up with matters that make discretely sequencing discovery in this MDL exceedingly difficult. To the extent the discovery Defendants seek to defer in a phased approach has little relationship to general causation, any benefit of deferring that discovery does not justify the case management costs in time and resources necessary to carry out Defendants' proposal. Moreover, the fluidity of corporate mergers and acquisitions and the longstanding and relatively common use of cross-functional teams in the pharmaceutical industry further cloud the prospect of efficient and effective discovery limited as Defendants propose.

Various of the Hill factors demonstrate the difficulty of separating general causation from other issues in these cases:

Alternative Explanations. Consideration of confounding factors and alternative explanations for the alleged injuries at issue will require analysis of the varied backgrounds of individual Plaintiffs' medical and social histories. Unlike a signature disease that occurs only following a particular exposure, the injuries alleged in this MDL are non-specific, meaning that they might have resulted from

any number of things. (*See, e.g.*, ECF No. 86-16, PageID #1056 ("dental erosion . . . [is a] multifactorial . . . disorder").)

But Defendants care less about case-specific discovery and more about narrowing discovery from them to those areas necessary to develop a record for a decision on general causation. On this record, however, information germane to general causation will likely go beyond the INDs, NDAs, clinical trials, and pharmacovigilance documents that Defendants seek to frontload and might well make additional research, data, or other information Defendants have relevant. Beyond these considerations tied to individual Plaintiffs, evaluation of alternative explanations promises to draw on the hard sciences, toxicology, or other disciplines. If so, it is difficult to see the benefit of limiting discovery to the few areas Defendants propose, even if drawing neat and enforceable bright lines to manage that process was possible. Considerably more information than Defendants suggest will likely bear on general causation.

Dose-Response Relationship. A dose-response relationship demonstrates that "the greater the exposure, the greater the risk of disease." *Reference Guide on Epidemiology* at 603. This factor depends on real-world experience and data that will address general causation in the particular circumstances at issue, removing some confounding factors or opportunities for misdirection. It might well also involve, among other things, any preclinical studies investigating the relationship between dose and adverse dental effects.

Biological Plausibility. This Hill factor builds on existing knowledge in the scientific literature exploring the mechanism through which the dental injuries at issue develop. Again, the parties hotly contest that mechanism and its specificity to Suboxone use. What matters for present purposes, however, is that the narrow categories of discovery on which Defendants propose to focus in the immediate short term will likely not provide sufficient information to address this factor.

Generally, the Hill criteria contemplate broad consideration of all relevant facts and data. In this MDL, Defendants' proposal threatens to limit the scientific evidence on general causation to an artificially narrow body of knowledge that would likely interfere with the search for the truth of general causation or render any such determination unreliable or too attenuated from real-world science. Nor does Defendants' proposal present a workable or efficient sequencing of discovery. It will do little to advance the overall progress of the MDL or the individual cases in it.

II. Bifurcation in Other MDLs

Again, general causation and its proof remain for another day. For present purposes, the foregoing discussion shows that, on the facts and circumstances of this case, general causation does not present a discrete body of knowledge that lies within easily identifiable or accessible repositories. As a result, it would be difficult to separate discovery on general causation from other generic issues that will apply across all cases in this MDL. Nor would it be efficient to do so here.

In making this determination, the Court considers the experience of other MDL courts. Plaintiffs and Defendants provide examples of other MDLs where courts bifurcated discovery or declined to do so. (ECF No. 61, PageID #654–57; ECF No. 86,

PageID #924–28.) From their examples, the Court concludes that bifurcation of discovery on general causation occurs in some MDLs but not in others; every MDL is different, and MDL courts enjoy broad discretion to manage pretrial proceedings to fit the needs of the particular cases. Without discussing each case the parties brief or those the Court has reviewed, two merit a brief mention.

First, Defendants rely on the court's decision in the *Onglyza* MDL to bifurcate general causation discovery and address it first. (*See* ECF No. 60-8; *In re Onglyza (Saxagliptin) & Kombiglyze XR (Saxagliptin & Metformin) Prod. Liab. Litig.*, No. 5:18-md-2809, ECF No. 179, PageID #1049 (E.D. Ky. 2018).) This decision carries particular weight because the *Onglyza* MDL judge also chairs the Judicial Panel on Multidistrict Litigation, and the Sixth Circuit affirmed her general causation ruling on appeal.

In *Onglyza*, the plaintiffs alleged that two diabetes medications containing the same active ingredient caused heart failure. The MDL court bifurcated discovery because "addressing general causation before considering plaintiff-specific issues will best ensure the most efficient resolution of these actions and use of the parties' and the Court's resources." (ECF No. 60-8, PageID #608.) After a Rule 702 hearing, the court excluded the plaintiffs' sole expert, a cardiologist, because he lacked the requisite qualifications to opine on general causation and relied on one clinical trial to the exclusion of other relevant studies and data, including more comprehensive follow-up analyses that contradicted the results of the original study. *In re Onglyza*, No. 5:18-md-2809, 2022 WL 43244, at *17–19 (E.D. Ky. Jan. 5, 2022).

Notably, the authors of the clinical trial study on which the plaintiffs' expert relied urged more research on the subject because any association between the drug and hospitalization for heart failure was "unexpected and should be considered within the context of multiple testing that may have resulted in a false positive result" and that a "class effect should not be presumed." *Id.* at *5. Consistent with that recommendation, multiple sets of researchers undertook more rigorous studies and meta-analyses and found no association between heart failure or increased risk of hospitalization for heart failure and the diabetes medications at issue. *Id.* After excluding the plaintiffs' expert, the MDL court granted summary judgment for the defendants, finding that the plaintiffs failed to produce admissible expert testimony on general causation. *In re Onglyza*, No. 5:18-md-2809, 2022 WL 3050665, at *7–14 (E.D. Ky. Aug. 2, 2022). On appeal, the Sixth Circuit affirmed, holding that "[t]he district court did not abuse its discretion" in concluding that the plaintiffs' expert was unreliable. *See In re Onglyza*, 93 F.4th 339, 346–47 (6th Cir. 2024).

This procedural history does little to inform the Court of the appropriate structure for discovery in this MDL. The Sixth Circuit did not directly address whether the MDL court abused its discretion by bifurcating discovery and proceeding first with general causation. Even reading the Sixth Circuit's decision as recognizing *sub silentio* that it was not an abuse of discretion to do so does not mean that it would have been an abuse of discretion *not* to bifurcate. After all, abuse of discretion review recognizes that trial judges select from a range of discretionary choices, any one of which might be proper. Fundamentally, *Onglyza* provides an example of an MDL

where, based on the broad discretion of the MDL court, the plaintiffs proceeded to test a general causation theory based on a single unreliable study and failed. But the record here looks nothing like the one in *Onglyza*. In this MDL, FDA and a number of professional medical associations take competing views of the science. That scientific disagreement supports following a more conventional discovery path, even if it later turns out that Plaintiffs cannot carry their burden to prove general causation.

Second, Defendants cite the Southern District of New York's decision to bifurcate discovery in the *Acetaminophen* MDL. As Plaintiffs here point out, the *Acetaminophen* Court "proposed, and the parties agreed, to conduct discovery related to general causation first; if the plaintiffs' experts on the issue of general causation survived Rule 702 motions, the remainder of discovery would proceed." *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, No. 22-md-3043, 2023 WL 8711617, at *2 (S.D.N.Y. Dec. 18, 2023). The court does not explain why it proposed to bifurcate discovery or why the parties agreed to do so. In ruling on the parties' motions under Rule 702, the court emphasized that the "epidemiological evidence is highly heterogenous, and major medical organizations and regulators have cautioned against drawing causal inferences from the existing body of scientific literature." *Id.* at *15. Notably, FDA had independently concluded that the scientific evidence was not yet able "to support a determination of causality" for ADHD from prenatal exposure to acetaminophen. *Id.* at *12–13.

In contrast, FDA required a warning for Suboxone in part based on its review of the scientific literature, holding out the prospect that Plaintiffs can prove general causation. Various medical groups cast doubt on their ability to do so. Further scientific study might support or refute either view. At bottom, the general causation theory is not so weak or tenuous at this early stage of the litigation that the just, speedy, and inexpensive administration of these proceedings requires focusing on it to the exclusion of other issues. In a world in which law follows the science and does not lead it, *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996), the apparent ongoing debate in the scientific community on the matter shows that general causation is not so clear or cleanly divisible from other general or case-specific discovery that bifurcation would materially expedite and simplify the proceedings in this MDL.

CONCLUSION

For the foregoing reasons, the Court **DENIES** Defendants' motion to bifurcate discovery. In doing so, the Court holds open the possibility—and, depending on the number of experts, the likelihood—that it will address Rule 702 motions in different groupings and not at one time. Because the needs of the case might appear different at that time, the Court declines to decide whether it will take any challenges under Rule 702 to experts on general causation first, but it might. For now, the Court will continue to manage the progress of discovery and, in consultation with counsel, set an appropriate schedule.

SO ORDERED.

Dated: June 24, 2024

J. Philip Calabrese
United States District Judge
Northern District of Ohio