UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

In re: Suboxone (Buprenorphine/ Naloxone) Film Products Liability Litigation This document relates to: All Actions	Case No. 1:24-md-03092-JPC MDL No. 3092 Hon. J. Philip Calabrese

DEFENDANT INDIVIOR INC.'S
PROPOSAL FOR PHASED DISCOVERY ON GENERAL CAUSATION

Indivior Inc. ("Indivior") files this Proposal for Phased Discovery on General Causation and in support thereof shows as follows:

I. Introduction

The Judicial Panel on Multidistrict Litigation consolidated these Suboxone® Sublingual Film ("Suboxone film") actions based in part on its recognition that "[t]he same factual questions regarding general causation, including mechanism of the alleged injury, are present in all cases." Feb. 5, 2024 JPML Transfer Order. If Plaintiffs cannot prove general causation – that Suboxone film is capable of causing the dental injuries alleged – all of their claims and all of their cases fail. As many courts have recognized, there is no point in undertaking the time and expense of developing and litigating other aspects of these cases if general causation cannot be established through scientifically reliable evidence. These courts have thus exercised

their discretion to dictate the sequence of discovery by ordering that general causation discovery and motion practice take place prior to other aspects of case development. As set out below, the data cited by Plaintiffs in support of general causation falls well short. To maximize efficiency and avoid unnecessary expenditure of time and resources, Indivior proposes that general causation discovery and motion practice take place prior to other aspects of case development.

II. Proposal for Phased Discovery and Motion Practice Prioritizing General Causation.

A. Focusing on General Causation Regarding Suboxone Film and Dental Adverse Events Makes Sense for Judicial Efficiency.

After the U.S. Food and Drug Administration ("FDA") issued its Drug Safety Communication regarding prescription drugs like Suboxone and certain dental adverse events, eleven medical associations analyzed the available scientific data. They not only found that the FDA recommendations lacked scientific support, but further found that it is "impossible to establish causality." If the thousands of physicians that comprise these eleven medical associations are correct, Plaintiffs' Suboxone film cases are not viable. Indivior proposes that initial discovery be focused on this key causation issue. This 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). "For effective discovery control, initial discovery should focus on matters – witnesses, documents, information – that appear pivotal." Manual for Complex Litigation ("MCL") § 11.422 (Fed. Jud. Ctr. 2004). Indivior requests precisely that: initial discovery focused on general causation closely followed by Rule

702 motion practice resolving the pivotal issue of whether, based on scientifically reliable evidence, Suboxone film is capable of causing the dental injuries claimed by Plaintiffs.

In seeking MDL consolidation, Plaintiffs specifically identified general causation as an issue common to all Suboxone film actions. The proposed phased discovery would provide for focused fact discovery on this pivotal issue common to all cases in this MDL, and then expert opinion discovery on that same issue. This discovery will be followed by Rule 702 motion practice, and then, a hearing to determine whether Plaintiffs can provide scientifically reliable testimony that Suboxone film is even capable of causing the complained of dental injuries. During this same time Plaintiffs would provide Plaintiff Profile Forms (with medical and dental records authorizations), which Indivior could use to initiate medical record discovery as necessary. Indivior has attached to this proposal as Exhibit 1 [Dkt No. 60-1] a description of the parameters of general causation discovery, and as Exhibit 2 [Dkt No. 60-2] a proposed time frame for conducting this discovery and concluding it with a Rule 702 hearing.

The substantial time and resources which would be spent on development of other issues will have been wasted if Plaintiffs ultimately fail to meet their general causation burden. In this litigation, the absence of a reliable scientific foundation to support general causation creates too great a risk of that very outcome. And because general causation must be determined at some point, there is no efficiency lost by prioritizing it through phased discovery.

B. The Data Cited by Plaintiffs Does Not Provide a Reliable Foundation for an Opinion that Suboxone Film Causes Dental Injuries.

On January 12, 2022, the FDA issued a Drug Safety Communication ("DSC") titled "*FDA Warns about dental problems with buprenorphine medicines dissolved in the mouth to treat opioid use disorder and pain: Benefits for use outweigh these risks and oral care can help.*" *See* Ex. 3 at Dkt No. 60-3. Less than two weeks later, a broad consortium of eleven medical societies and associations having a depth of knowledge of and experience with both transmucosal buprenorphine and the patient population it benefits sent a letter urging a full retraction of this DSC. This letter addressed the FDA's conclusions and recommendations as follows:

- The DSC "has **not been based on solid research evidence**"
- "In this epidemiological circumstance, it is **not possible to conclude** a causal relationship …"
- "**impossible** to establish causality"
- "the mechanism of causation is **implausible**"
- "**neither** of these reasons [for oral care recommendations] has **scientific support**"
- Xerostomia (reduced saliva) "is **caused by hundreds of medications**"
- Asked for retraction of the DSC because of the "**flawed analysis regarding causation**"

Ex. 4, January 24, 2022 Correspondence to FDA (emphasis added) at Dkt No. 60-4.

The FDA based its DSC statements on its review of 305 case reports from its FDA Adverse Event Reporting System (FAERS) database, out of over two million users of transmucosal buprenorphine. Ex. 3, p. 6 at Dkt No. 60-3. General causation

cannot reliably be drawn from this data, because as noted by the medical organizations, 91% of these patients had prior dental problems, raising the possibility that the reported dental event stemmed from a pre-existing condition. The median time to diagnosis of the dental event was two years following medication use, an extensive time period during which myriad alternative and unaccounted for exposures could have caused or contributed to the event. The consortium correctly stated that this circumstance "makes it impossible to establish causality." Ex. 4, p. 2 at Dkt No. 60-4. And 63% of those patients had only one tooth affected, casting doubt on any postulated causal mechanism stemming from the medicine, which if valid would likely affect more than one tooth.

The significant flaws observed in the FDA's analysis set out in its DSC reflects the more fundamental scientific principle that case reports cannot provide a reliable basis for inferring a cause-effect relationship. But Plaintiffs rely on this same data – reports taken from the FAERS database – to support their claim of an established causal relationship between Suboxone film exposure and dental adverse events. *See, e.g.,* Thomas Goldner Complaint, Ex. 5, ¶¶ 74 – 86 (listing adverse event reports) at Dkt No. 60-5. Plaintiffs cite a published case report – which as the name suggests is simply a publication addressing a single case report of patient using the tablet version of Suboxone. *See* Ex. 5, ¶ 65 (citing Suzuki J and Park EM, *Buprenorphine/naloxone and dental caries: a case report.* Am. J. Addict. 2012-Sep-Oct; 21(5): 494-5) at Dkt No. 60-5. Plaintiffs also rely on a case series report which in its conclusion theorized only that "buprenorphine/naloxone…may be a contributing factor in the alteration of the

tooth microbial profile and/or the pH to promote dental caries, similar to what has been previously reported in patients who use methamphetamine." Suzuki J, Mittal L, and Woo S. *Sublingual Buprenorphine and Dental Problems: A Case Series.* Prim. Care Companion CNS Disord. 2013; 15(5) (Oct. 2, 2013). This case series, built upon case reports of tablet users, suffers from the same scientific deficiencies as case reports in general. Like the case reports on which it is based, it is not reliable evidence of causation.

Plaintiffs also cite a December 2022 letter to the editor in support of their claimed causal relationship between Suboxone film and dental adverse events. *See* Ex. 5, ¶ 97 (citing Etminan M, Rezaeianzadeh R, Kezouh A, et al. *Association Between Sublingual Buprenorphine-Naloxone Exposure and Dental Disease.* JAMA (Dec. 13, 2022) at Dkt No. 60-5, Ex. 6 at Dkt No. 60-6). But that Letter to the Editor only involved a retrospective assessment of vastly different patient populations. Observational retrospective analyses such as this one do not study populations that were prospectively controlled for exposure to other risk factors that could contribute to the outcome at issue (here, dental disease), which limits the ability to draw reliable conclusions from them. The Letter to the Editor itself noted "possible unmeasured confounding" as a limitation. *See* Ex. 6 at Dkt No. 60-6. Further, this assessment compared significantly divergent cohorts: Suboxone users (treatment for opioid use disorder), transdermal buprenorphine users (treatment for chronic pain), and oral naltrexone users (treatment for alcohol use disorder), and the authors themselves

noted as a limitation their own "inability to ascertain the indication for the medications." *See id.*

In a letter published by JAMA lodging criticisms at the methodology underlying this Letter to the Editor, the comparison of these vastly different patient populations was characterized as "problematic." Ex. 7, Watson D, Etminan S, Gastala N, *Comment and Response: Sublingual Buprenorphine-Naloxone Exposure and Dental Disease*, JAMA April 11, 2023) at Dkt No. 60-7. As detailed by this Response Letter, transdermal buprenorphine is typically prescribed for pain management and is explicitly not recommended for OUD treatment. Oral naltrexone is more commonly recommended for alcohol use disorder treatment. In contrast to these patient groups, the patient population with a history of OUD encompasses "a host of other factors associated with [OUD] that can affect oral health." *Id.* (citing Baghaie H, Kisely S, Forbes M, Sawyer E, Siskind DJ. *A Systemic Review and Meta-Analysis of the Association Between Poor Oral Health and Substance Abuse.* Addiction. 2018; 112(5)-765-769. doi: 10.1111/add.13754). This comparison of different groups by the Letter to the Editor authors "greatly limit their conclusions," according to the authors of the Response Letter. In addition, the reliability of the database from which the authors of this letter drew their data is unclear. Last, many Suboxone users in that cohort used tablet, not film. These multiple analytical flaws render any conclusions drawn in or from this letter to the editor unreliable.

As the foregoing makes clear, Plaintiff's only identified basis for suggesting a causal relationship between Suboxone film and dental adverse events is (1) case

reports, and (2) a scientifically flawed letter to the editor. There is "widespread recognition among federal courts that 'case reports alone cannot prove causation.'" *DeGidio v. Centocor Ortho Biotech Inc.*, 3 F. Supp. 3d 674, 684 (N.D. Ohio 2014) (citing *In re Meridia*, 328 F. Supp. 2d 791, 808 (N.D. Ohio 2004)). This is because, among other things, case reports:

- "make little attempt to screen out alternative causes for a patient's condition"
- do not compare the reported phenomena to a rate of occurrence in the general population or in a defined control group
- do not isolate and exclude potential alternative causes
- do not investigate or explain the mechanism of causation; and
- often omit relevant facts about the patient's condition.

Id. Indeed, as the *DeGidio* court and the Eleventh Circuit have observed, "case reports raise questions; they do not answer them." *Id.* (citing *McLain v. Metabolife Int'l, Inc.,* 401 F.3d 1233, 1254 (11th Cir. 2005)).

C.. Recent Pharmaceutical MDL Decisions Strongly Support Prioritized Resolution of General Causation Prior to Other Case Development.

A district court for the Eastern District of Kentucky overseeing a pharmaceutical MDL determined that phasing discovery to first address general causation was appropriate, noting that the issue was "a critical issue in this [litigation], common to all actions." Ex. 8, *In Re: Onglyza (Saxagliptin) and Kombiglyze XR (Saxagliptin and Metformin) Products Liability Litigation,* MDL 2809, Case Management Order No. 1 at Dkt No. 60-8. The court recognized as a threshold issue that if plaintiffs could not establish general causation, "the parties

will not be required to undergo the time and expense of further discovery and litigation" and thus recognized that "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." *Id.*

In that litigation, Plaintiffs based their claim of general causation on a randomized controlled trial ("RCT") referred to by its acronym "SAVOR." *See In re Onglyza (Saxagliptin) and Kombiglyze (Saxagliptin and Metformin) Products Liability Litigation,* 93 F.4th 339, 343 (6th Cir. 2024). That study found a statistically significant difference between the exposed population and placebo on hospitalizations for heart failure. *Id.* The Reference Manual on Scientific Evidence (Third Ed., 2011) describes the significance of RCTs in relation to establishing causation in pharmaceutical cases as follows:

> To determine whether an agent is related to the risk of developing a certain disease or an adverse health outcome, we might ideally want to conduct an experimental study in which the subjects would be randomly assigned to one of two groups: one group exposed to the agent of interest and the other not exposed. After a period of time, the study participants in both groups would be evaluated for the development of the disease. ***This type of study, called a randomized trial, clinical trial, or true experiment, is considered the gold standard for determining the relationship of an agent to a health outcome or adverse side effect***. Such a study design is often used to evaluate new drugs or medical treatments and is the best way to ensure that any observed difference in outcome between the two groups is likely to be the result of exposure to the drug or medical treatment.

Id., Reference Guide on Epidemiology, p. 555 (emphasis added). Thus, in the *Onglyza* litigation plaintiffs had an RCT – the gold standard – supporting general causation, and the district court nevertheless prioritized the resolution of general causation to avoid unnecessary expenditure of resources in the event plaintiffs could not meet

their burden of establishing it. And as it turned out, following phased discovery, briefing and argument on general causation, the court determined that plaintiffs had failed to carry their burden, and the 6th Circuit very recently upheld that determination. *In re Onglyza*, 93 F.4th at 342.

Similarly, in the *Acetaminophen* MDL, "the 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 Prod. Liab. Litig.*, No. 22MC3043 (DLC), 2023 WL 8711617 at *2 (S.D.N.Y. Dec. 18, 2023). In that litigation, plaintiffs' experts – all of whom were qualified to render the opinions offered – offered opinions based on their review of the body of scientific evidence which included multiple epidemiological studies. *Id.* at *15 (plaintiff's experts have drawn causation inferences from epidemiological evidence on acetaminophen and fetal development issues). Even with this body of scientific literature pertaining to the general causation issues raised by plaintiffs' claims, the *Acetaminophen* court determined that it would be prudent to resolve general causation before spending potentially unnecessary time and resources on case development unrelated to that issue. In a thorough and detailed analysis, that court upheld defendants' Rule 702 challenge to the general causation testimony offered by plaintiffs. *Id.* at *49.

Here, in terms of scientifically reliable data, Plaintiffs cite to far less material than that proffered in *Onglyza* and *Acetaminophen* to support general causation. Simply put, none of the data or material cited by Plaintiffs could provide a reliable

foundation for general causation expert testimony under Rule 702 and case authority applying it. Plaintiffs devote multiple paragraphs in their complaints to exaggerated portrayals of unrelated civil and criminal proceedings involving Suboxone film, but cite to only three publications – two of which are based on case reports involving only Suboxone *tablets*, and the third which *fails to differentiate* between tablet and film – relating to the alleged association between Suboxone *film* and the injuries claimed in this litigation. Plaintiffs mischaracterize the updated Suboxone film label as communicating that "Suboxone film causes serious and potentially irreversible dental injuries." Ex. 5 ¶ 146 at Dkt No. 60-5. But the FDA-approved label actually states that "Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), ***have been reported*** following the use of transmucosal buprenorphine-containing products." Ex. 9, § 5.13 (Suboxone film label) (emphasis added) at Dkt No. 60-9. That cases "have been reported" may raise questions, but it does not answer them. The label does not suggest, and the FDA never concluded, that Suboxone film exposure causes dental injuries. And the state of the science does not support the claim that it does.

II. Specific Proposal for Phased Discovery on General Causation

Parameters on the categories of discovery that relate to general causation can be easily defined. They would include actual scientific evidence such as clinical trial data, adverse event reports of dental adverse events, and submissions to scientific or governmental organizations relating to the question of whether Suboxone film can cause the dental injuries claimed in these cases. By contrast, internal company documents that are not within these categories are generally not relevant to the

question of general causation. *See, e.g., In re Zoloft (Sertralinehydrochloride) Prods. Liab. Litig.*, 176 F. Supp. 3d 483, 497 (E.D. Pa. 2016) *aff'd,* 858 F.3d 787 (3d Cir. 2017) ("[I]nternal Pfizer documents, including discussions among Pfizer's own epidemiologists and other scientists analyzing certain epidemiological studies…may be relevant to questions of Pfizer's knowledge and actions if Zoloft were found to cause birth defects, but do not raise a genuine issue of material fact as to causation.").

Indivior can work with Plaintiffs' counsel to develop a schedule for the completion of general causation discovery. To initiate that discussion, Indivior has attached as Exhibit 2 [Dkt No. 60-2] a proposed schedule for fact and expert discovery and Rule 702 motion practice.

III. Conclusion

A consortium of medical associations and societies with extensive experience with transmucosal buprenorphine urged the FDA to retract its safety communication regarding dental problems because of its "flawed analysis regarding causation" and absence of "solid research evidence." Shortly after publication of the Etminan Letter to the Editor, a group of scientists and doctors found it necessary to publish a response identifying major analytical flaws with its methodology and conclusions. Yet Plaintiffs ask this Court to conclude that this same scientifically unreliable material supports the conclusion that Suboxone film can cause their claimed dental injuries.

Opioid use disorder has impacted millions of individuals in the United States. Numerous studies have demonstrated buprenorphine's efficacy in retaining patients in treatment and reducing illicit opioid use. The consortium of medical associations

and societies which responded to the FDA communication and whose members understand this drug and use it to help patients consider it to be "the gold standard for care" which helps OUD patients "begin a sustained recovery and get their lives back." Ex. 4, p. 1 at Dkt No. 60-4. This Consortium and the authors of the Response Letter to the Editor both expressed concern that scientifically flawed conclusions about this life-saving medication and dental injuries could result in negative public health effects by discouraging its use. Plaintiffs' claim that Suboxone film caused them "disability," "loss of capacity for enjoyment of life," "loss of ability to earn money" and "losses in the future" (e.g., Ex. 5, ¶ 156 at Dkt No. 60-5) – all based on the same body of material dismissed by experts in the field as scientifically unreliable - will only amplify these negative public health effects. This presents a compelling and urgent reason to resolve the issue of general causation as expeditiously as possible. For this reason and to avoid the unnecessary expenditure of resources on other aspects of these cases, the question of whether reliable scientific evidence supports general causation should be addressed through phased discovery focused on general causation.

Dated: April 11, 2024

Respectfully submitted,

BOWMAN AND BROOKE LLP

By: */s/ Randall L. Christian*
Randall L. Christian

2901 Via Fortuna Drive, Suite 500
Austin, Texas 78746
Tel: (512) 874-3811
Fax: (512) 874-3801
Randall.Christian@bowmanandbrooke.com

Denise A. Dickerson
SUTTER O'CONNELL
3600 Erieview Tower
1301 East 9th Street
Cleveland, Ohio 44114
Tel: (216) 928-2200
Fax: (216) 928-4400
ddickerson@sutter-law.com

Attorneys for Defendant Indivior Inc.

CERTIFICATE OF SERVICE

Per Appendix B, ¶ 14 of the Northern District of Ohio's Electronic Filing Policies and Procedures Manual, I hereby certify that on April 11, 2024, the foregoing *Defendant Indivior Inc.'s Proposal for Phased Discovery on General Causation* was electronically filed with the Clerk of Court using the CM/ECF system, and notice of this filing will be electronically transmitted to all counsel of record by operation of the Court's electronic filing system.

/s/ Randall L. Christian
Randall L. Christian