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

IN RE SUBOXONE (BUPRENORPHINE/NALOXONE) FILM PRODUCTS LIABILITY LITIGATION This Document Applies to All Cases	)	Case No. 1:24-md-03092-JPC MDL No. 3092 Judge J. Philip Calabrese

Plaintiffs' Opposition to Defendant's Proposal for Phased Discovery on General Causation

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Orders

Statutes and Regulations

Other Authorities

INTRODUCTION

The Court should deny Defendant Indivior Inc.'s request for an Order bifurcating general and case-specific discovery. The *only* way Defendant's promised efficiency occurs is if the Court *presupposes* Defendant will prevail on its inevitable Rule 702 and 56 motions. *Any* other outcome will add years to this litigation as the parties are forced to restart the balance of general and case-specific discovery following Rule 702 motion practice. Most importantly, the likelihood of Defendant prevailing is remote given that decades of scientific publications support Plaintiffs' allegations that the highly acidic substances like Suboxone film cause dental erosion and decay. The only thing phased discovery would accomplish is unnecessarily prolonging this MDL and wasting resources in direct contravention of growing complaints about the protracted nature of MDLs. It is for this reason that the vast majority of MDL courts decline to adopt bifurcation. The Court should decline to adopt it here.

BACKGROUND

Defendant Indivior Inc. filed a Proposal for Phased Discovery on General Causation (ECF No. 61) on April 11, 2024, and a Supplement to the proposal (ECF No. 66) on April 23, 2024. Contending the "categories" of phased discovery are "easily defined," Defendant's proposal limits the "relevant" categories to "actual scientific evidence such as clinical trial data, adverse event reports…and submissions to scientific or governmental organizations…." ECF No. 61, PageID #: 657. This is where the dispute begins.

Defendant's promise that the line of demarcation between causation and liability discovery is "easily defined" is belied by the way pharmaceutical companies actually operate. These companies typically are composed of multiple cross-functional teams. For example, R&D may sit on a committee with Marketing so that the business arm understands not only the anticipated time to launch, but also the risks associated with the product. Does Defendant contemplate that for these cross-functional team members, the marketing portion of a scientist's custodial file is off limits? Or worse, that the marketing employee may not testify *at all* about what R&D reported (*e.g.*, "we may have a problem with tooth decay given the acidity of the product."). Similarly, do the categories of permissible discovery include production of emails (internal or external) involving Defendants' scientists, SAS data from clinical trials, epidemiology, or communications with the "independent" third-party associations Defendant touts in its submission—none of which are included in its proposal? *See* ECF No. 60-1 (limiting "Document Discovery on General Causation" to FDA submissions, pivotal clinical trials, and pharmacovigilance documents for the Suboxone tablet and film).

In truth, "[t]here is no neat line dividing information relevant to general causation …undoubtedly leading to myriad disputes whether certain information, search terms, interrogatories, or deposition questions are sufficiently relevant to one and not the other." *Dean v. Pfizer, Inc.,* Case No. 419-CV-00204, 2020 WL 12032895, at *3 (S.D. Ind. Dec. 9, 2020). The same will be true here.

LAW AND ARGUMENT

Defendant's bifurcation proposal is based on the premise that "Plaintiffs cannot prove general causation." ECF No. 61, PageID #: 648. This premise is faulty in several respects. Setting aside that plaintiffs are not required to prove general causation in a complaint, ample scientific evidence supports general causation here. In fact, decades of scientific research establish a plausible mechanism for Plaintiffs' injuries: highly acidic products, like Suboxone film, cause tooth erosion. As discussed more fully below, courts agree that proof of mechanism is sufficient to establish general causation.

Mounting adverse-event reports (just one of which can be sufficient to require a label change) and peer-reviewed literature also establish a causal connection between Suboxone film use and a decline in oral health. *See, e.g.*, Dunham Complaint, Case No. 1:24-sf-65636, ECF No. 1, at ¶¶ 66–67, 69, 71, 75–88, 98. Despite knowing of this connection, Defendants delayed amending the Suboxone film label to warn about dental decay until FDA mandated the change. *Id.* at ¶ 95. Importantly, per 21 C.F.R. § 201.57(c)(6), FDA will not require a Section 5 warning about a "clinically significant hazard" without "reasonable evidence of a causal association with a drug." Here there is reasonable evidence of a causal association between Suboxone film use and the type of dental injuries Plaintiffs allege. It is this causal association that prompted FDA to mandate a label change.

Beyond the scientific evidence that already exists to prove general causation, MDL courts also overwhelmingly refuse to bifurcate discovery due to the inefficiencies and costs it adds to litigation.

I. Defendant's bifurcation request should be denied because there is reliable scientific support that Suboxone film causes dental injuries.

A. Proof of mechanism proves general causation.

Defendant's *lone* scientific justification for bifurcation revolves around the purported absence of epidemiological studies. ECF No. 61, PageID#: 653. Specifically, it contends an epidemiological analysis published in the Journal of the American Medical Association in December 2022 is flawed and that the absence of any other epidemiology signals the near certain demise of Plaintiffs' claims. *Id.* 653–54. Defendant is wrong. The law in this Circuit (and District) overwhelmingly establishes that proof of mechanism and differential diagnosis are also sufficient to prove *both* general and case-specific causation. In short, assuming Defendant's allegations were true, a *total absence* of epidemiology is *irrelevant* where the plaintiff established biological plausibility (*i.e.*, mechanism) and medical causation (via a differential diagnosis). Examples are numerous:

- *In re Heparin Prod. Liab. Litig.*, 803 F. Supp. 2d 712, 728–29 (N.D. Ohio 2011) (expert's causation testimony based on mechanism was admissible and sufficient to defeat summary judgment; court "decline[d] to categorically exclude plaintiffs' scientific evidence solely on the basis that it is not epidemiological in nature");
- *Ruth v. A.O. Smith Corp.*, No. 1:04-CV-18912, 2006 WL 530388, at *17 (N.D. Ohio Feb. 27, 2006) (denying defendant's causation motion where the "overriding theme…is that plaintiffs do not have sufficient epidemiological or other evidence to prove general causation");
- *In re Meridia Prod. Liab. Litig.*, 328 F. Supp. 3d 791, 801 (N.D. Ohio 2004) (noting that "courts have continued to reject a mandate for epidemiological evidence…to establish general causation when other methods of proof are available");
- *Hardyman v. Norfolk & W. Ry. Co.*, 243 F.3d 255, 262 (6th Cir. 2001) (reversing the lower court's exclusion of expert's differential diagnosis;

holding that differential diagnosis is an acceptable alternative to epidemiological studies);

- *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 178 (6th Cir. 2009) ("This court recognizes differential diagnosis as an appropriate method for making a determination of causation for an individual instance of disease.") (citation omitted) (cleaned up);
- *Z.H. by and through Hutchens v. Abbott Labs., Inc.*, 2017 WL 5461626, *4 (N.D. Ohio Jan. 18, 2017) (finding no requirement that a party must offer epidemiologic evidence to establish causation);
- *In re Welding Fume Prod. Liab. Litig.*, No. 1:03-CV-17000, MDL No. 1535, 2005 WL 1868046, at *10–11, 35 n.82 (N.D. Ohio Aug. 8, 2005) (collecting cases supporting that epidemiological evidence is not required to prove general causation where other evidence of general causation exists; holding that mechanism evidence can be used to show general causation).

In fact, no court in this District has ever dismissed a case *solely* because of a lack of epidemiological evidence where the plaintiff established mechanism.

Although Defendant turns a blind eye to it, proof of mechanism can be sufficient scientific evidence to prove general causation. For example, in *In re Meridia*, the Court noted that "no requirement exists that a party *must* offer epidemiologic evidence to establish causation." 328 F. Supp. 2d at 800. To the contrary, all evidence of general causation must be considered, including whether there is a plausible biologic mechanism for the product causing a particular injury. *See e.g.*, *In re Welding Fume*, 2005 WL 1868046 at *11 and *36 (holding that MDL court "must examine 'non-epidemiological lines of evidence' of general causation, including: biological plaus[i]bility, animal studies, human clinical studies, case reports and case series, medical textbooks, and other treatises").

Defendant is wrong to ignore proof of mechanism throughout its proposal. The utter absence of any concession that mechanism—coupled with a viable differential

diagnosis—is sufficient to evade a Rule 702 challenge, underscores the flaw in Defendant's argument: namely, the *only* way it achieves its so-called "efficiency" is by ignoring the law in this Circuit *and* decades of scientific literature supporting Plaintiffs' claims.

B. Decades of scientific publications showing proof of mechanism establish a causal association between acidic products like Suboxone film and dental decay.

Although not a Rule 702 challenge, Defendant's proposal implicates the Rule via its contention the Court will ultimately exclude the PLC's experts. Not so. Mechanistic experts are routinely allowed to testify where their theory is predicated upon "generally accepted principles" in the scientific community. *Redmond v. United States*, 194 F. Supp. 3d 606, 616 (E.D. Mich. 2016) ("An expert's opinion relating to specific technologies, processes, or mechanisms at issue in the case will not necessarily be precluded because the expert lacks training or experience with those particular subjects, where the expert's opinion as to the operation or effect of specific mechanisms is based on the application of generally accepted principles of his discipline and flow from his investigation of the facts of the case.").

The hallmark of "generally accepted" science is peer-reviewed literature that aligns with the expert's mechanism theory. *See, e.g.*, *Decker v. GE Healthcare Inc.*, 770 F.3d 378, 392–93 (6th Cir. 2014) (holding district court did not abuse its discretion in admitting expert testimony on causation where the mechanism theory offered was subjected to peer review and publication and was generally accepted in the scientific community); *Williams v. United States*, No. 17-CV-13118, 2019 WL 11718796, at *6 (E.D. Mich. Oct. 9, 2019) (finding mechanism expert's testimony on

causation admissible where her theory was "published in relevant medical journals and subject to peer review"). According to the patent for Suboxone film, "[m]ost preferably the local pH of the film composition is about 3.5."[1] Here, Defendant's proposal ignores decades of peer-reviewed scientific research establishing a causal association between acidic products (like Suboxone film) and dental decay.

For nearly 75 years, the scientific community recognized the mechanism underlying Plaintiffs' allegations: that acid erodes teeth is by no means groundbreaking:

Year	Publication	Excerpt Evidencing Mechanism
1960	Lillian N. Ellis & Elizabeth J. Dwyer, *The Influence of Dietary Factors upon the Composition of Mineralized Tissues and upon the Susceptibility of Enamel to Erosion in vivo: I. Phosphorus*, 72 J. Nutrition 224 (1960) (Ex. 1)	"When canned orange juice, pH 3.7 to 3.8 was provided as the fluid, erosion of the enamel layer occurred and to a greater extent on the lower calcium diet...when neutralized orange juice was provided no erosion was observed..."
1962	John A. Gray, *Kenetics of the Dissolution of Human Dental in Acid*, 42 J. Dental Rsch. 633 (1962) (Ex. 2)	"The dissolution of enamel in acid occurs as a result of reaction between the hydrogen ion and the inorganic material which forms the principal part of the enamel."
1963	Geoffrey H. Sperber & Michael G. Buonocore, *Effect of Different Acids on Character of Demineralization of Enamel Surfaces*, 42 J. Dental Rsch. 707 (1963) (Ex. 3)	"...at a constant pH, different acids not only show remarkable variation in dissolving capacity but also demonstrate an ability markedly to increase or decrease the demineralizing potential of the acid buffers when added to them. These variations in demineralizing ability at a constant pH appear to be related more to differences in the chemical structure of the acids than to the other factors."

[1] Sublingual and buccal film compositions, US Patent 8,475,832 B2, column 12, line 33–34.

Year	Publication	Excerpt Evidencing Mechanism
1966	G.N. Jenkins, *The Influence of Environmental Fluids on Enamel Solubility*, 45 J. Dental Rsch. 662 (1966) (Ex. 4)	"... the greater the buffering power [of saliva], the more difficult it is for the acid in the mouth to lower the pH below the critical figure. This is the usual view of salivary buffering power as having a protective effect for the tooth."
1973	James L. Mc Donald, Jr. & George K. Stookey, *Laboratory Studies Concerning the Effect of Acid-Containing Beverages on Enamel Dissolution and Experimental Dental Caries*, 52 J. Dental Rsch. 211, 215 (1973) (Ex. 5)	"Furthermore, all of the commercial products evaluated seemed to cause enamel dissolution, regardless of the presence or absence of sucrose in the product … thus the majority of the damage must be attributed to the constituent acids..."
1975	Basil G. Bibby & S.A. Mundorff, *Enamel Demineralization by Snack Foods*, 54 J. Dental Rsch. 461 (1975) (Ex. 6)	"The amount of enamel destroyed by salivary fermentation of snack foods and confections was not dependent on their sugar content; starch, flavoring agents, and other components also played a part. Most enamel destruction was produced by fruit-flavored candies in which the inherent acid or high sugar concentration or both inhibited bacterial fermentation."
1978	Carl J. Kleber & Mark S. Putt, *Enamel Dissolution by Various Food Acidulants in a Sorbitol Candy*, 57 J. Dental Rsch. 447 (1978) (Ex. 7)	"In water, the potential of the food acids to demineralize enamel was directly proportional to their acidity."
1980	T. Koulourides & B. Cameron, *Enamel remineralization as a factor in the pathogenesis of dental caries*, 9 J. Oral Pathology 255 (1980) (Ex. 8)	"The development of higher tooth resistance to acid through demineralization and remineralization was demonstrated experimentally on bovine enamel presoftened in acid, treated with fluoride, exposed to the oral environment, and finally exposed to the acid buffers for development of subsurface lesions."

Year	Publication	Excerpt Evidencing Mechanism
1983	John J. Sheridan, *Acid trench effect of a surgical splint used following orthognathic surgery*, 41 J. Oral Maxillofacial Surgery 201 (1983) (Ex. 9)	"Because the mucosa and tongue cannot cleanse the covered surfaces of the teeth or coat them with buffered saliva, the acid in the beverages is free to cause decalcification."
1986	J.M.P.M. Borggreven, et al., *Dissolution and precipitation reactions in human tooth enamel under weak acid conditions*, 31 Archives Oral Biology 139 (1986) (Ex. 10)	"It was concluded that precipitation of brushite, and a preferential dissolution of Na and Mg compounds from the enamel both play a role in the dissolution-precipitation reactions in dental enamel during acid attack"
1987	M.V. Patel, et al., *Effect of Acid Type on Kinetics and Mechanism of Dental Enamel Demineralization*, 66 J. Dental Rsch. 1425, 1430 (1987) (Ex. 11)	"...when the values of the driving force function (i.e., the ion activity product prevailing at the solution-crystal interface) and the surface kinetic factor, k', are known, hydroxyapatite dissolution rates can be predicted for any given weak acid situation. It is believed that the present approach can contribute significantly to the understanding of and rational approaches to the control of caries."
1990	M.J. Larsen, *Chemical events during tooth dissolution*, 69 J. Dental Rsch. 634 (1990) (Ex. 12)	"The solubility of enamel powder increases dramatically with a decrease of pH ... concluded that any dissolution of enamel is caused by an undersaturation with respect to enamel apatite."
2000	J.A. Hughes, et al., *Effects of pH and concentration of citric, malic and lactic acids on enamel, in vitro*, 28 J. Dentistry 147 (2000) (Ex. 13)	"This study has shown that under highly controlled conditions the erosion of enamel by solutions of dietary acids is influenced by the interplay of pH, acid concentration and presence of calcium."

Year	Publication	Excerpt Evidencing Mechanism
2001	M. Eisenberger & M. Addy, *Evaluation of pH and erosion time on demineralisation*, 5 Clinical Oral Investigations 108 (2001) (Ex. 14)	"In the current study the effect of various pH values of citric acid and erosion time on erosion depth and subsurface demineralisation of human enamel was studied." "Erosion depth clearly depended on the pH value of the acid and the contact time."
2003	Colin Dawes, *What Is the Critical pH and Why Does a Tooth Dissolve in Acid?*, 69 J. Canadian Dental Ass'n 722, 723 (2003) (Ex. 15)	"In people with low salivary concentrations of calcium and phosphate, the critical pH may be 6.5, whereas in those with high salivary calcium and phosphate concentrations, it may be 5.5.3 The fluid phase of dental plaque contains much higher concentrations of calcium and phosphate than does saliva,4 and its critical pH may be as low as 5.1.Thus, the critical pH is not a constant, because the levels of calcium and phosphate in plaque fluid vary among individuals. The more calcium and phosphate that are present in a solution, the lower its critical pH."
2004	A. Lussi, et al., *The Role of Diet in the Aetiology of Dental Erosion*, 38 Caries Rsch. 34 (2004) (Ex. 16)	"Acids of intrinsic and extrinsic origin are thought to be the main etiologic factors for dental erosion. There is evidence that acidic foodstuffs and beverages play a role in the development of erosion. However, the pH of a dietary substance alone is not predictive of its potential to cause erosion as other factors modify the erosive process."
2006	Thorburg Jensdottir, et al., *Effects of Calcium on the Erosive Potential of Acidic Candies in Saliva,* 41 Caries Rsch. 68,73 (2006) (Ex. 17)	"The modified candy released more than 13 mmol/l [mg/dl] of calcium into saliva, resulting in a lower critical pH, and considerably lower erosive potential than the control."

Year	Publication	Excerpt Evidencing Mechanism
2007	Barry M. Owens & Michael Kitchens, *The Erosive Potential of Soft Drinks on Enamel Surface Substrate: An* In Vitro *Scanning Electron Microscopy Investigation*, 8 J. Contemp. Dental Prac. 1 (2007) (Ex. 18)	"As verified by microscopic evaluation, all test beverages displayed enamel dissolution in the following order: Red Bull® (pH 3.41) >Gatorade® (pH 3.12) >Coca-Cola Classic® (2.49) >Diet Coke® (3.12)."
2008	Leslie A. Ehlen, et al., *Acidic beverages increase the risk of in vitro tooth erosion,* 28 Nutrition Rsch. 299, 303 (2008) (Ex. 19)	"Both the concentration and strength on an acid can influence the degree of erosion; the pH is determined by both concentration and strength of the acid in solution."
2009	Ana Carolina Magalhães, et al., *Insights into preventive measures for dental erosion*, 17 J. Applied Oral Sci. 75, 76 (2009) (Ex. 20)	"The frequent and excessive consumption of acids is associated with an increased risk for dental erosion."
2010	Birgül Azrak, et al., *Influence of Bleaching Agents on Surface Roughness of Sound or Eroded Dental Enamel Specimens*, 22 J. Esthetic Restorative Dentistry 391 (2010) (Ex. 21)	"Materials and Methods: ... To provoke erosive damage, the enamel specimens were incubated for 10 hours with apple juice (pH=3.4)." "Results: The study demonstrated that exposure to an acidic bleaching agent (pH=4.9) resulted in a higher surface roughness ($p = 0.043$) than treatment with a high peroxide concentration (pH=6.15). If the enamel surface was previously exposed to erosive beverages, subsequent bleaching may enhance damage to the dental hard tissue."
2011	Tais Scaramucci, et al., *In vitro evaluation of the erosive potential of orange juice modified by food additives in enamel and dentine,* 39 J. Dentistry 841, 848 (2011) (Ex. 22)	"The addition of lower amounts of calcium (10 mmol/l) to the orange juice (group CLP) was able to reduce dental erosion in the pH-stat and in the demineralization and erosion remineralization models."
2012	Adrian Lussi, et al., *Analysis of the erosive effect of different dietary substances and medications,* 107 British J. Nutrition 252, 262 (2012) (Ex. 23)	Tests revealed "a significant reduction of [tooth enamel] for soft drinks, sports drinks, the energy drink (Red Bull), juices (except for carrot juice), fruits, and salad dressings."

Year	Publication	Excerpt Evidencing Mechanism
2014	J.F. Tahmassebi, et al., *The effects of fruit smoothies on enamel erosion*, 15 Eur. Archives Paediatric Dentistry 175 (2014) (Ex. 24)	"The smoothies tested were acidic and had high titratable acidity. They produced a significant erosion of enamel in vitro."
2014	Nicola X. West & Andrew Joiner, *Enamel mineral loss*, 42 J. Dentistry S2 (2014) (Ex. 25)	"Dental erosion can be the result of acid from intrinsic sources, such as gastric acids, or extrinsic sources, in particular from the diet and consumption of acidic foods and drinks."
2018	Alex J. Delgado, et al., *Potential erosive effect of mouthrinses on enamel and dentin*, Acad. Gen. Dentistry 75, 77 tbl.2 (2018) (Ex. 26)	Listerine Total Care with pH of 3.43 had more mean mass loss from enamel as compared to other mouthrinses with a high value pH.
2019	Eun-Jeong Kim & Bo-Hyoung Jin, *Effects of Titratable Acidity and Organic Acids on Enamel Erosion In Vitro*, 19 J. Dental Hygiene Sci. 1 (2019) (Ex. 27)	"The titratable acidity and the citric and malic acid contents of the fruits could be crucial factors responsible for enamel erosion. Therefore, fruit-based drinks should be regarded as potentially erosive."
2021	Imran Farooq & Amr Bugshan, *The role of salivary contents and modern technologies in the remineralization of dental enamel: a narrative review*, 9 F1000 Rsch. 171 (2021) (Ex. 28)	"Human enamel once formed cannot be biologically repaired or replaced. Saliva has a significant role in remineralization of dental enamel. It not only has a buffering capacity to neutralize the oral cavity's low pH generated after acidic encounters, but also acts as a carrier of essential ions, such as fluoride, calcium and phosphate, which have a positive role in enamel's remineralization."
2023	Adrian Lussi, et al., *The erosive effect of various drinks, foods, stimulants, medications and mouthwashes on human tooth enamel*, 133 Swiss Dental J. 440, 441 (2023) (Ex. 29)	"The capacity of a simple acidic solution to dissolve dental hard tissue depends on its pH… citric acid was added and the pH value was significantly lowered down to 3.2, we found a significant softening of the enamel surface." "Some medications and sweets with pH values as low as 2.7 showed a large erosive potential."

This scientific evidence proves the mechanism by which Plaintiffs' claim Suboxone film caused their injuries.

But that's not all. Xerostomia, or dry mouth, is a known side effect of buprenorphine.[2] Saliva is the mouth's natural protection against acidic insult; it acts as a weak base to neutralize acid.[3] As a buffering agent, saliva protects and maintains oral tissues and protect teeth from acid's effects.[4] So an acidic product like Suboxone introduces acid to tooth enamel without the natural protective effects of saliva: the xerostomia caused by buprenorphine leaves the user's mouth without the power to fight back.

With this type of evidence available at the outset, there is no basis to presume, as Defendant does, that Plaintiffs cannot prove general causation. Consequently, there is no basis to bifurcate general-causation discovery.

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[2] *See* Kumar R, et al., *Buprenorphine*, StatPearls (updated Nov. 30. 2023) (available at) (last accessed May 23, 2024) ("Additional adverse effects of buprenorphine include … dry mouth…") (available at https://www.ncbi.nlm.nih.gov/books/NBK459126/) (last accessed May 23, 2024); Urzan C., Safety Alert: Dental Issues with Transmucosal Buprenorphine, Cleveland Clinic Clincal Rx Forum, 2023 Vol. 11, Issue 1 ("A common side effect, which has become more apparent with increased use of buprenorphine, is xerostomia or dry mouth, a contributing factor to various dental problems.") (available at https://www.clevelandclinicmeded.com/medicalpubs/pharmacy/Clinical_Rx_Forum_Jan_Feb_2023.pdf) (last accessed May 23, 2024).

[3] *See* Helm JF, et al., *Acid Neutralizing Capacity of Human Saliva*, Gastroenterology 1982;83:69–74 (available at https://www.gastrojournal.org/article/S0016-5085(82)80286-2/fulltext) (last accessed May 23, 2024).

[4] Pandey P, et al. *Estimation of salivary flow rate, pH, buffer capacity, calcium, total protein content and total antioxidant capacity in relation to dental caries severity, age and gender*, Comtemp Clin Dent. 2015 Mar; 6(Suppl 1): S65–S71 (available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4374323/#:~:text=According%20to%20Neil%2C%201978%2C%5B,%E2%80%9330%20mg%2F100%20ml) (last accessed May 22, 2024).

C. Observational retrospective analysis is a reliable methodology to prove general causation.

Contrary to Defendant's allegations, there *is* epidemiological evidence establishing an increased risk of tooth erosion and extraction following exposure to Suboxone film. *See* Dunham Compl., Case No. 1:24-sf-65636, ECF No. 1 at ¶ 98. As stated above, Defendants recognize such evidence exists but claim the published evidence is insufficient given it involved a retrospective review (published in JAMA) observing a statistically significant increased risk to oral health following exposure to Suboxone. At the outset, JAMA is one of, if not *the* preeminent peer-review journal in the country. Nonetheless, Indivior claims the publication is "scientifically flawed" based on its underlying methodology—*i.e.*, it is a retrospective review.[5] ECF No. 61, PageID#: 654. But identifying the potential weaknesses of a scientific source in the context of litigation does not render such source inadmissible or uninformative; instead, that is merely a contention reserved for cross-examination.

A retrospective review like that criticized by Defendant here and cited in Plaintiffs' complaints is permissible evidence of general causation. *In re Avandia Mktg., Sales Pracs. & Prod. Liab. Litig.*, No. 2007-MD-1871, MDL No. 1871, 2011 WL 13576, *15 (E.D. Pa. Jan. 4, 2011) (denying the defendant's motion to exclude expert witnesses who based their opinions, in part, on meta-analyses of multiple studies and retrospective analyses of published literature). In finding each expert's methodology

[5] Insurance retrospective reviews involve a comparisons of large-scale insurance database comparing the offending agent to a second drug that is known not to cause the studied harm. The studies typically analyze ICD-9 codes across the database to both adequately power and evaluate a fixed Odds-Ratio.

reliable under *Daubert* and Rule 702, the *Avandia* MDL court acknowledged that both meta-analyses and retrospective observations offer advantages that epidemiological studies lack—namely the ability to adequately power a study. *Id.* at *8–9. As such, this evidence may be reliably used by experts opining on general causation. *See id.* at *15 (finding that "the experts' methods are the product of reliable principles and methods" and "[d]ifferences in conclusions go to the weight of the evidence, and not to its admissibility"). When the time comes (it is not yet here), Plaintiffs' experts may, or may not, rely on retrospective studies. But for purposes of today, the suggestion that such studies are patently deficient—so as to justify bifurcation—is patently wrong.

D. A single adverse-event report can establish sufficient evidence of causation to warrant strengthening a drug's warning label.

Next, Defendant argues that reports of adverse events published in FDA's FAERS database "cannot provide a reliable basis for inferring a cause-effect relationship." Proposal, ECF No. 61, PageID #: 651. This assertion is flat-out wrong. In fact, FDA's Regulatory Guidance for Industry establishes that a single adverse event *can* establish a causal association sufficient to require drug manufacturers to update its label.[6]

The FDCA grants FDA the authority to regulate drug labeling. 21 U.S.C. § 355(b)(1)(F). In 2007, Congress amended the FDCA to "require a manufacturer to change its drug label based on safety information that becomes available after a

[6] *See* FDA Guidance for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1995), at 10 (available at https://www.fda.gov/media/71188/download) (last accessed May 9, 2024).

drug's initial approval." *Wyeth v. Levine*, 555 U.S. 555, 567 (2009). Based on this amendment, *Wyeth* recognized that it is the drug manufacturer, as opposed to FDA, that bears ultimate responsibility for a label's contents. *Id.* at 568. To ensure drug manufacturers can carry out their responsibility, the FDCA empowers them to alert FDA of "Changes Being Effected" (CBE) to the label.

CBE regulations allow a manufacturer to change a drug's label without prior FDA approval, "if the change is designed to 'add or strengthen a…warning where there is 'newly acquired information' about the 'evidence of a causal association between the drug and a risk of harm.'" *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1673 (2019) (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). "Newly acquired information" includes "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (*e.g.*, meta-analyses)." *In re Taxotere Prod. Liab. Litig.,* 508 F. Supp. 3d 71, 81 (E.D. La. 2020) (citing 21 C.F.R. § 314.3).

Discussing the scope of "newly acquired information," the Supreme Court reiterated that it includes data triggering any *one* of the four warning categories subsumed within 21 C.F.R. § 201.57(c). *See Albrecht*, 139 S. Ct. at 1673. This includes data evidencing "*some basis* to believe there is a *causal relationship* between the drug and the occurrence of an adverse event." 21 C.F.R. § 201.57(c)(7) (emphasis supplied) (cleaned up). In short, where a manufacturer obtains newly acquired information evidencing "some basis" of a causal relationship, it *must* use the CBE process to make a label change.

Commenting on newly acquired information, FDA's Guidance for Industry establishes that a *single* well-documented post-marketing adverse-event report constitutes newly acquired information that may evidence a safety signal requiring action by the manufacturer, including a label change.[7] Given this guidance, the adverse-event reports detailed in the various complaints documenting a decline in oral health temporally associated with Suboxone film use are more than "some basis" for establishing a causal connection between Suboxone film and the injuries Plaintiffs allege. *See e.g.,* Dunham Compl. at ¶¶ 75–88 (alleging 146 adverse events reported to FDA regarding Suboxone).

E. The assertions of medical associations financially tied to Defendants does not undermine the scientific basis of Plaintiffs' allegations.

Indivior's leading support for insisting Plaintiffs' allegations are "not viable" is a letter co-signed by various medical associations who declared it "impossible to establish causality" between drugs like Suboxone and "certain adverse events." ECF No. 61 at PageID #: 648. Indivior fails to note that (at least) eight of the eleven signatories have an overt connection to one or more Defendants in this case.

For example, Defendants sponsored sessions for conferences held by the American Academy of Addiction Psychiatry (AAAP),[8] the American Society of

[7] *See id*. at 10 (available at https://www.fda.gov/media/71188/download) (last accessed May 9, 2024).

[8] *See, e.g.*, AAAP, 25th Annual Meeting and Symposium (2014) (listing Reckitt Benckiser Pharmaceuticals—now Defendant Indivior PLC—among the sponsors) (available at https://www.aaap.org/wp-content/uploads/2014/11/2014-AM-Program-Final.pdf) (last accessed May 19, 2024).

Addiction Medicine (ASAM),[9] and the College of Psychiatric and Neurologic Pharmacists (CPNP).[10] Defendants also are affiliated with members of several of the organizations' boards of directors, including AAAP,[11] ASAM,[12] the American Osteopathic Academy of Addiction Medicine (AOAAM),[13] the Association for Multidisciplinary Education and Research in Substance Use and Addiction (AMERSA),[14] the California Society of Addiction Medicine (CSAM),[15] and the

[9] *See, e.g.*, ASAM, Sponsors, ASAM 55th Annual Conference (2024) (listing Indivior Inc. as the Platinum Sponsor) (available at https://annualconference.asam.org/sponsors.asp?pfp=Sponsors) (last accessed May 19, 2024).

[10] *See, e.g.*, CPNP, Annual Meeting Schedule (2019) (listing Indivior as a sponsor) (available at https://aapp.org/ed/meeting/2019/schedule) (last accessed May 19, 2024).

[11] Board of Directors, American Academy of Addiction Psychiatry (available at https://www.aaap.org/about/board-of-directors/) (last accessed May 20, 2024) (listing David Lott, MD as the APA Liaison on the AAAP Board of Directors). *See also* Medications for Opioid Use Disorder (MOUD), Lott Behavioral Health (available at https://www.lottbehavioral.com/moud) (last accessed May 20, 2024) (listing Suboxone and Sublocade as two of the three available addiction treatments at David Lott's practice).

[12] *See e.g.*, ASAM Board of Directors Relationships with Industry and Other Entities (2020) (available at https://cdn-links.lww.com/permalink/jam/a/jam_00_00_2020_04_06_white_jam-d-20-00038_sdc3.pdf) (last accessed May 19, 2024) (listing Kelly J. Clark, MD and Edward C. Covington receiving financial benefit from Indivior and Melissa Welmer, DO as an Indivior consultant).

[13] Leadership, American Osteopathic Academy of Addiction Medicine (available at https://www.aoaam.org/Leadership) (last accessed May 20, 2024) (listing Marla Kushner, DO as a past AOAAM president). *See also* Marla Kushner, DO, Bicycle Health (available at https://www.bicyclehealth.com/team-members/marla-kushner-do) (last accessed May 20, 2024) (listing Marla Kushner, DO, as a practician at Bicycle Health, which exclusively treats addiction and exclusively uses Suboxone).

[14] *Clinician Perspectives on Delivering Medication Treatment for Opioid Use Disorder during the COVID-19 Pandemic: A Qualitative Evaluation*, National Library of Medicine (Mar. 2, 2023) (available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10417321/) (last accessed May 20, 2024) (author Andrew J. Saxon "reports personal fees from Indivior... and serves on the board of directors for the American Society of Addiction Medicine, the Association for Multidisciplinary Education and Research in Substance Use and Addiction, and the International Society of Addiction").

[15] Board of Directors, California Society of Addiction Medicine (available at https://csam-asam.org/about/about-csam/board-of-directors/) (last accessed May 20, 2024) (listing Matthew A. Torrington, MD as the Chair of the Committee on Opioids). *See also* Matthew A.

American College of Academic Addiction Medicine (ACAAM).[16] In most cases, these affiliations included payments from Defendants to the board members.

Several of the signatory organizations also have obvious financial motives for supporting Defendants. AAAP and ASAM are two of the few organizations authorized to provide the training necessary for doctors to prescribe Suboxone;[17] the ASAM eLearning Center is supported by an unrestricted educational grant from Indivior;[18] AMERSA worked on a Phase 3 clinical trial for Reckitt Benckiser Pharmaceuticals (now Defendant Indivior PLC);[19] and the NEJM Group, a division of the Massachusetts Medical Society (MMS) focused on publications, is sponsored by Reckitt Benckiser.[20] It is no surprise that organizations inextricably tied to

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Torrington, OpenPaymentsData.CMS.gov (available https://openpaymentsdata.cms.gov/physician/116660) (last accessed May 20, 2024) (showing that Matthew A. Torrington has received consulting fees and food and beverage money from Indivior).

[16] 2024–2025 Board of Directors, American College of Academic Addiction Medicine (available at https://www.acaam.org/board-of-directors) (last accessed May 20, 2024) (listing Louis E. Baxter as a Director at Large of the ACAAM). *See also* Louis E Baxter, OpenPaymentsData.CMS.gov (available at https://openpaymentsdata.cms.gov/physician/618355) (last accessed May 23, 2024) (showing that Louis E. Baxter has received consulting fees from Indivior).

[17] Substance Abuse and Mental Health Services Administration, Professional Medical Membership and Training and Accreditation/Approval Organizations (last updated Mar. 27, 2024) (available at https://www.samhsa.gov/medications-substance-use-disorders/training-requirements-mate-act-resources/professional-medical-membership-training-accreditation-organizations) (last accessed May 19, 2024).

[18] ASAM, Advanced Buprenorphine Education, ASAM eLearning (available at https://elearning.asam.org/Advanced-Buprenorphine-Education) (last accessed May 19, 2024).

[19] Powerpoint presentation by then-CEO Shaun Thaxter (available at https://www.indivior.com/resources/dam/id/178/H1%202017%20results%20presentation.pdf at page 22) (last accessed May 19, 2024).

[20] NEJM Journal, Companies that Sponsor Distribution, NEJM Journal Watch (available at https://www.jwatch.org/about/sponsor-distribution) (last accessed May 19, 2024).

Defendants' business would attack FDA's Drug Safety Communication regarding buprenorphine and claim causality is "impossible" to prove. ECF No. 61, PageID #: 648.

Finally, individual members of these organizations have personal financial interests in keeping patients on Suboxone film for life (rather than for a shorter period of stabilization and tapering). These doctors make money by treating this drug like insulin and continuing to prescribe it to patients forever. Thus, it comes as no surprise that members of these organizations would seek (unsuccessfully) to reverse the FDA's determination that a warning about dental risks was needed.

In sum, this letter in which Defendant places so much stock by no means renders the Suboxone film cases scientifically unviable, especially where there is extensive scientific support for Plaintiffs' allegations.

Moreover, the inherent bias of these so-called "independent" medical associations underscores the problem with Defendant's proposed bifurcation plan (explored more fully in section II.D below). Specifically, where does the Court draw the line to bifurcate "general cause" from merits discovery? Defendant draws that line at: "actual scientific evidence such as clinical trial data, adverse event reports…and submissions to scientific or governmental organizations…." *Id*. at PageID#: 657. But that line *precludes* third-party discovery aimed at these "independent" associations to explore an assortment of topics that will establish their biased opinion—like the financial relationship with Defendants, whether the organization is made up of key

opinion leaders for Defendants, whether Defendants' personnel serve on the boards or influenced the organizations' statement, to name a few.

If Defendant's proposal were accepted, Defendants would proceed to Rule 702 motion practice without Plaintiffs having the opportunity to conduct discovery to into whether these organizations—and specifically the decision-makers who authorized signing on to this letter—are truly "independent." And while Defendants may prefer not to shine the broad light of day on their secret work with these groups, that sunlight is necessary to establish that the groups' statement amounts to little more than Defendants themselves insisting "our product is safe." Based on what Plaintiffs were able to swiftly establish through preliminary online research, one can only imagine the treasure trove that exists in corporate documents to demonstrate Defendants' financial ties to these organizations. Limiting Plaintiffs to the narrow category of documents that Defendant proposes would undercut Plaintiffs' ability to properly cross-examine Defendants' experts for bias.

II. MDL courts routinely reject proposals like Defendant's for their obvious inefficiencies and costs.

A. Unified discovery is the norm.

Contrary to Defendant's position, courts widely reject phased discovery plans like the one Defendant proposes. *Dean*, 2020 WL 12032895, at *2 ("Bifurcated discovery is not the norm"). The vast majority of MDL courts—including most recently a court in a pharmaceutical MDL concerning a drug where the FDA ordered a Section 5 label change (*In re Tepezza*)—reject bifurcated discovery.

Date	MDL	Bifurcation
6/21/2005	*In re Vioxx Prod. Liab. Litig.,* Case No. 2:05-MD-01657, MDL No. 1657 (E.D. La.), ECF No. 472, pp. 4–6 (Pretrial Order No. 17 permitting discovery to proceed in individual cases)	**No**
7/3/2006	*In re Mirapex Prod. Liab. Litig.*, Case No. 07-1836, MDL No. 1836 (D. Minn.), ECF No. 26, p. 1 (adopting the schedule previously agreed on in 15 individual cases opening all fact discovery and providing date for expert disclosures without bifurcation)	**No**
12/5/2005	*In re Accutane Prod. Liab. Litig.,* Case No. 8:04-md-2523, MDL No. 1626 (M.D. Fla.), ECF No. 14, PageID#: 180	**No**
8/7/2007	*In re Ortho Evra Prod. Liab. Litig.*, Case No. 1:06-40000, MDL No. 1742 (N.D. Ohio), ECF No. 148, PageID#: 740 (CMO 20 permitting generic expert discovery to proceed simultaneously with fact discovery in bellwethers)	**No**
5/22/2008	*In re Trasylol Prod. Liab. Litig.*, Case No. 1:08-md-1928, MDL No. 1928 (S.D. Fla.), ECF No. 60, p. 1 (Pretrial Order No. 4 setting initial schedule without bifurcation)	**No**
9/24/2008	*In re Gadolinium-Based Contrast Agents Prod. Liab. Litig.*, Case No. 1:08-GD-50000, MDL No. 1909 (N.D. Ohio), ECF No. 180, PageID#: 1633 (CMO 8 contemplating simultaneous close of general causation and case-specific expert discovery).	**No**
10/13/2010	*In re Yasmin and Yaz (Drospirenone) Mktg., Sales Practices and Prod. Liab. Litig.*, Case No. 3:09-md-02100, MDL No. 2100 (S.D. Ill.), ECF No. 1329, PageID#: 4849 (Amended CMO No. 24 providing bellwether process and case specific core discovery and further discovery when a trial pool is established)	**No**
2/24/2010	*In re Chantix (Varenicline) Prod. Liab. Litig.*, Case No. 2:09-cv-02039, MDL No. 2092 (N.D. Ala.), ECF No. 25, pp. 6–9; 21–23 (Pretrial Order No. 4 ordering fact discovery to proceed in tandem expert discovery on general causation and liability)	**No**
10/03/2012	*In re Pradaxa (Dabigatran Etexilate) Prod. Liab. Litig.*, Case No. 3:12-md-02385, MDL No. 2385 (S.D. Ill.), ECF No. 42 (CMO No. 6 Unified Case Management Plan)	**No**

Date	MDL	Bifurcation
10/19/2012	*In re Zimmer NexGen Knee Implant Prod. Liab. Litig.*, Case No. 1:11-cv-05468, MDL No. 2272 (N.D. Ill.), ECF No. 653 (Parties' Revised Joint Submission Regarding Representative Trial Plan)	**No**
4/1/2013	*In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.,* Case No. 12-MD-2342, MDL No. 2342 (E.D. Pa.), ECF No. 287 (discovery not bifurcated)	**No**
8/1/2013	*In re EI DuPont De Nemours and Co. C-8 Personal Injury Litig.*, Case No. 2:13-md-2433, MDL No. 2433 (S.D. Ohio), ECF No. 30 (CMO No. 2 implementing discovery phase to include merits and general causation discovery)	**No**
10/1/2013	*In re Tylenol (Acetaminophen) Mktg., Sales Practices, and Prod. Liab. Litig.*, Case No. 2:13-md-92456, MDL No. 2436 (E.D. Penn.), ECF No. 68.	**No**
11/6/2014	*In re Testosterone Replacement Therapy Prod. Liab. Litig.*, Case No. 1:14-cv-01748, MDL No. 2545 (N.D. Ill.), ECF No. 407, PageID#: 5364 (denying the defendants' request to bifurcate causation and merits discovery).	**No**
10/30/2015	*In re Cook Med., Inc. IVC Filters Mktg., Sales Practices and Prod. Liab. Litig.*, Case No. 1:14-ml-02570, MDL 2570 (S.D. Ind.), ECF No. 8, PageID#: 29 (order denying the defendant's motion to bifurcate noting it could "complicate the scope of bifurcated discovery and generate avoidable discovery disputes")	**No**
12/24/2015	*In re Ethicon Inc. Power Morcellator Prod. Liab. Litig.*, Case No. 15-d-2652, MDL No. 2652 (D. Kan.), ECF No. 80, pp. 3–6; 9–14 (Scheduling Order No. 1)	**No**
4/26/2016	*In re Fluroquinolone Prod. Liab. Litig.*, Case No. 15-2642, MDL No. 2642 (D. Minn.), ECF No. 155, p. 1 (initial Case Management Plan opening all fact discovery without bifurcation)	**No**
11/29/2016	*In re Zostavax (Zoster Vaccine Live) Prod. Liab. Litig.*, Case No. 18-md-2848, MDL No. 2848 (E.D. Penn.), ECF No. 94, p. 1 (Pretrial Order No. 47 opening all fact discovery); ECF No. 691, p. 3 (Pretrial Order No. 346 aligning general causation and case-specific expert discovery)	**No**
5/1/2017	*In re Invokana (Canagliflozin) Prod. Liab. Litig.*, Case No. 3:16-md-2750, MDL No. 2750 (D.N.J.), ECF No. 218, PageID#: 1098 (CMO No. 20)	**No**

Date	MDL	Bifurcation
7/21/2017	*In re Taxotere (Docetaxel) Prod. Liab. Litig.*, Case No. 16-md-02740, MDL No. 2740 (E.D. La.), ECF No. 669, p. 4, ¶¶ 6, 8 (CMO No. 3 aligning fact and expert discovery)	**No**
9/7/2017	*In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices and Prod. Liab. Litig.*, Case No. 3:16-md-2738, MDL No. 2738 (D.N.J.), ECF No. 693, PageID#: 5118 (CMO No. 9 setting discovery deadlines without bifurcation)	**No**
4/11/2018	*In re Nat'l Prescription Opiate Litig.*, Case No. 1:17-CV-2804, MDL No. 2804 (N.D. Ohio), ECF No. 232, PageID #1095–1101 (CMO No. 1)	**No**
5/18/2018	*In re Proton-Pump Inhibitor Prod. Liab. Litig.,* Case No. 2:17-md-2789, MDL No. 2789 (D.N.J.), ECF No. 116, PageID#: 1322, ¶ 2 (denying the defendants' motion to consider general causation and preemption before conducting case-specific fact discovery)	**No**
5/20/2019	*In re Aqueous Film-Forming Foams Prod. Liab. Litig.*, Case No. 2:18-mn-2873, MDL No. 2873 (D.S.C.), ECF No. 99, p. 1 (CMO No. 4)	**No**
6/20/2019	*In re 3M Combat Arms Earplug Prod. Liab. Litig.*, Case No. 3:19-md-2885, MDL No. 2885 (N.D. Fla.), ECF No. 452, pp. 2–3 (CMO No. 2)	**No**
4/30/2021	*In re Elmiron (Pentosan Polysulfate Sodium) Prod. Liab. Litig.*, Case No. 2:20-md-02973, MDL No. 2973 (D.N.J.), ECF No. 35, PageID#: 346 (CMO No. 7 opening initial discovery); ECF No. 42, PageID#: 441 (CMO No. 9 ordering parties to implement bellwether discovery)	**No**
12/3/2021	*In re Paraquat Prod. Liab. Litig.*, Case No. 3:21-md-3004, MDL No. 3004 (S.D. Ill.), ECF No. 587, PageID#: 1604–05 (CMO No. 12)	**No**
11/11/2022	*In re Abbott Labs., et. al., Preterm Infant Nutrition Prod. Liab. Litig.*, Case No. 1:22-cv-00071, MDL No. 3026 (N.D. Ill.), ECF No. 278, PageID# 3674 (order declining to adopt defendants' proposed discovery schedule)	**No**
7/6/2023	*In re Hair Relaxer Mktg., Sales Practices, and Prod. Liab. Litig.,* Case No. 1:23-cv-00818, MDL No. 3060 (N.D. Ill.), ECF No. 146 (minute entry declining "to adopt Defendants' proposal (Dkt. 125 at 6) requesting prioritizing 'general causation' discovery")	**No**

Date	MDL	Bifurcation
12/28/2023	*In re Uber Technologies, Inc. Passenger Sexual Assault Litig.*, Case No. 3:23-md-03084, MDL No. 3084 (N.D. Cal.), ECF No. 175, pp.7–8 (Pretrial Order No. 5)	**No**
1/2/2024	*In re Paragard IUD Prod. Liab. Litig.*, Case No. 1:20-md-02974, MDL No. 2974 (N.D. Ga.), ECF No. 605, pp. 2–3 (CMO and Second Amended Scheduling Order).	**No**
1/26/2024	*In re Social Media Adolescent Addiction/Personal Injury Prod. Liab. Litig.*, Case No. 4:22-md-03047, MDL No. 3047 (N.D. Cal.), ECF. No. 579, p. 1 ("The request for early resolution of the general causation issue was DENIED for the reasons articulated on the record.")	**No**
5/1/2024	*In re Tepezza Mktg., Sales Practices, and Prod. Liab. Litig.*, Case No. 1:23-cv-03568, MDL No. 3079 (N.D. Ill.) (the court denied defendant's proposal for staggering expert and merits discovery at the CMC on May 1) (transcript has been ordered and will supplement this filing once received)	**No**

Simply put, bifurcation is not the norm.

B. Bifurcation results in extended delays in the progress of an MDL.

When bifurcation is adopted it invariably adds *years* to the MDL. Three examples are noteworthy. Each case lasted nearly a decade, with two of the three resulting in denial of the defendant's Rule 702 motion. They include:

- *In re Bair Hugger Forced Air Warming Devices Prods. Liab. Litig.*, MDL No. 15-2666, CMO 13 (ECF No. 108). The Court bifurcated discovery and ultimately granted defendant's Rule 702 motion to exclude. On appeal, the Eighth Circuit reversed the court's order excluding the plaintiff's experts and remanded the case. *Id. at* ECF No. 2155. Upon returning to the district court, defendants *again* sought to exclude plaintiff's experts, which the court denied. ECF No. 2387, p. 2. The case is nearly a decade old and has yet to be tried. Defendant's lead counsel in this MDL also represents the *Bair Hugger* defendant. *See* ECF No. 2384.

- *In re Roundup Prods. Liab. Litig.*, 16-md-02741, MDL No. 2741 (N.D. Cal.). In 2016, the court bifurcated discovery. ECF No. 25, p. 1. Two years later,

the court denied defendant's motion to exclude the plaintiff's general-causation expert. 390 F. Supp. 3d 1102 (N.D. Cal. 2018). The MDL is nearly eight years old and currently boasts over 18,000 docket entries.

- *In re Incretins Prods. Liab. Litig.,* MDL No. 2452 (JPML, Aug. 26, 2013). Originally transferred to the Southern District of California in August of 2013, the court bifurcated preemption, general causation, and merits discovery. Eight-and-a-half years, and two trips to the Court of Appeals (one of which involved the Ninth Circuit *reversing* the district court's discovery limitations) later, the case finally ended. *In re Incretin-Based Therapies Prods. Liab. Litig.*, 721 Fed. Appx. 580, 584 (9th Cir. 2017). Although Defendants prevailed on their preemption arguments, the intervening discovery limitations added *years* to the litigation and required an intermediate trip to the Ninth Circuit regarding the line of demarcation for general causation and fact discovery.

These cases vividly demonstrate the risk associated with bifurcation—*even where the defendant prevails in part*—but especially where its Rule 702 efforts are unsuccessful. In each case, bifurcation added *years* and hundreds of thousands of dollars in costs to the litigation as the parties haggled over the scope of "general" versus "merits" discovery, often based on incomplete records to defend Rule 702 motions. The clear takeaway from this path is this: courts should almost never, and only in exceedingly rare situations, resort to a bifurcated schedule.

C. The outlier cases Defendant cites are distinguishable from this case given that Plaintiffs here posit a plausible mechanism theory.

The two lone cases Defendant cites to support its bifurcation argument are not relevant to the facts of this MDL. The first, *In re Acetaminophen–ASD-ADHD Product Liability Litigation*, was bifurcated by *agreement* of the parties. No. 22MC3043 (DLC), 2023 WL 8711617 at *2 (S.D.N.Y. Dec. 18, 2023). The *Tylenol* plaintiffs alleged that they suffered autism spectrum disorder and attention-deficit hyperactivity disorder as a result of maternal ingestion of Tylenol during pregnancy. There was no

mechanism posited and no warning on the Tylenol label about such injuries. Under those particular circumstances, it is understandable that all parties would benefit from an early decision on general causation, which is likely why the plaintiffs agreed to proceed with bifurcated discovery and prioritize 702 motions. Here, by contrast, there is a plausible biologic mechanism, no attenuation of injury, and the FDA has required a Section 5 warning about the precise injuries Plaintiffs allege.

The second case Defendant cites, *In re Onglyza*, also sheds no light on how this case should proceed. First, *Onglyza* concerned saxagliptin—one of many drugs in a class of diabetic medications (DPP-4 inhibitors). *In re Onglyza (Saxagliptin) & Kombiglyze XR (Saxagliptin & Metformin) Prod. Liab. Litig.*, No. 5:18-MD-2809-KKC, 2022 WL 43244, at *1 (E.D. Ky. Jan. 5, 2022). The labels of Onglyza and Kombiglyze, two diabetes drugs that contained saxagliptin, were changed after a single study (SAVOR) showed an uptick in hospitalizations for heart failure. *Id. a*t *4. No DDP-4 inhibitor besides saxagliptin had a label change following the SAVOR study, and—critically—there was no explanation as to why a single drug would cause an injury that other drugs in the class did not. *Id.*

Importantly, the SAVOR authors cast doubt on their results by expressly acknowledging that the study's finding regarding hospitalization for heart failure "should be considered within the context of multiple testing that may have resulted in a false positive result." *Id.* at *10. The authors also urged further investigation and noted the finding "need[ed] to be confirmed in other ongoing studies, and that a class effect should not be presumed." *Id.* Following the SAVOR study, five sets of

researchers conducted observational studies of saxagliptin. *Id.* at 5. None found an association between the drug and heart failure. *Id.* Meta-analyses similarly found no increased risk. *Id.* The FDA also required studies of other DPP-4 inhibitors, none of which replicated SAVOR's result regarding heart failure. *Id*. at 5. Under those unique circumstances—where the scientific authority on which the plaintiffs relied acknowledged that it was likely an outlier and explicitly urged further study—the court's determination to bifurcate the proceedings was justified.

The district court in *Onglyza* excluded the plaintiffs' lone general causation expert because he relied on *exclusively* on the SAVOR study to establish general causation, ignoring the numerous other studies that made no such finding as well as the SAVOR authors' own statements as to its limitations. *Id. a*t *15. Further, the plaintiff's expert could not name a single other source or expert agreeing with the proposition that this one drug in the class caused heart failure. *Id*.

This case is different. Like *Tylenol*, *Onglyza* included no mechanism evidence. Here, by contract, the published, peer-reviewed literature establishing that acid rots teeth is extensive. *See* Section I.B). This is in stark contrast to *Onglyza*, where the SAVOR study's own authors questioned the finding of increased risk of heart failure and further studies failed to corroborate it. *Id.* at *10. *Onglyza* is also not instructive because the FDA issued a warning about a single drug in a class, where the other drugs in that class were not associated with similar purported injuries and there was no explanation as to why. *Id*. at *5. Here, the FDA mandated warnings for the entire

class of buprenorphine drugs that are dissolved in the mouth. Attempting to liken this MDL to *Onglyza* is trying to put a square peg into a round hole.

D. There is no clean way to cleave merits discovery from general-causation discovery; Defendant's proposal would cause problems at every step.

Bifurcating discovery is inefficient, in part because evidence on liability and causation are inextricably intertwined, and there is "no neat line dividing information relevant to general causation and specific causation." *Dean v. Pfizer, Inc.*, No. 419CV00204, 2020 WL 12032895, at *3 (S.D. Ind. Dec. 9, 2020). These overlaps would lead to inevitable, myriad, and extended disputes over whether discovery is related to one or the other. *Id.*; *Maysonet*, 2020 WL 3100840, at *3, n.3. Some of the ways that attempting to draw such a line would impact discovery follow:

***Custodians*:** Discovery in MDL litigation starts with identifying relevant corporate custodians. Corporate custodians drive *all* discovery that follows because these custodians represent the vast majority of documents a defendant will collect, review, and produce. Bifurcation artificially culls the list of relevant custodians by eliminating large groups of otherwise relevant persons. This presents two problems: First, it ensures the custodial production will occur twice (one round identifying "causation" employees and one identifying "merits" custodians, some of whom will be the same people). Second, it creates the very real situation that *relevant general-causation* documents *will not be produced.* As noted above, a drug company's employees often work on cross-functional teams (*e.g.,* scientists often interact with marketing to advance the corporation's goals). At the same time, the companies often employ aggressive document-destruction policies leading to situations where the

production across custodial files is not uniform but varies based on individual employee practices. Practically, that works as follows: scientist emails marketer commenting on issues related to the toxicity of Suboxone. Scientist does not save the document and, as a result, it is purged from the system per the company's document-destruction policy. But the marketer does save that communication, so it still exists in the company's system. Because bifurcation precludes plaintiffs from collecting the marketer's custodial file, that document is *never* produced during the "general cause" phase. This deprives Plaintiffs of relevant evidence.

Search Terms: All modern complex litigation relies on some form of electronic-assisted review to collect documents. Whether that be search terms or Technology Assisted Review, the parties will use a process to identify relevant documents. Bifurcation artificially limits relevant search terms. This not only ensures that search-term negotiations will occur *twice*—with the corresponding delay as the parties haggle over merits v. general-cause terms—but also requires a defendant to search, review, and produce many of the same terms twice.

***Document Review*:** Bifurcation ensures document production, and its corresponding review, will occur twice. Defendants will contend that Plaintiffs may receive only documents specifically relevant to general causation, from limited custodians, in response to Plaintiffs' document requests. Because bifurcation artificially limits the universe of responsive documents, reviewers—who tag documents based on document requests—may overlook documents related to merits

discovery given there will be no underlying document request related to merits discovery. As such, *every* custodian's file will need to be reviewed twice.

***Depositions*:** Depositions are particularly problematic. First, bifurcation ensures that *all* general-causation witnesses will be deposed twice—once for causation and once for merits. Defendant's proposal ignores this conundrum, glossing over the practical reality created by the Rules. Specifically, is the PLC required to preserve time from its seven hours based on little more than a hunch of the scope of the custodian's merits production? Or does the PLC get two rounds of seven-hour depositions (with the corresponding requirement to travel to and pay for videography and court reporting again)? And what if "causation" emails wade into "merits" identifying interaction with non-scientists? May the PLC reuse that email in the second deposition or take the deposition of the non-scientist during "causation" discovery. *None* of this is outlined in Defendant's proposal.

Third-Party Discovery: Defendant's proposal for bifurcating general-causation discovery does not include any allowance for conducting discovery of third parties. As noted above, Plaintiffs reasonably anticipate conducting discovery of the "independent" medical organizations that rushed to Defendants' aid when the FDA mandated a warning for buprenorphine dissolvables and will likely determine that other third-party discovery is appropriate. And what if one or more of Defendants prevail on their forthcoming personal-jurisdiction motions? Are Plaintiffs permitted to obtain discovery from the companies that designed, distributed, and marketed this

drug at its launch and for years thereafter? Can the Court make that determination without knowing anything about where the corporate documents are housed?

***Motion Practice*:** The list of unanswered questions will invariably cause one thing: waves of motion practice as the parties haggle over the scope of relevant "causation" discovery.

Rather than streamline the discovery process, Defendant's proposal will create myriad complications and require that twice as much time (or more) is required to plod through the scads of work to be done in this MDL. Front-loading discovery on a particular issue—particularly when the resulting motion and hearings could prove unsuccessful—would result in delays in other discovery if Defendants are unsuccessful and will result in increased costs. *Gonzalez v. Texaco, Inc.,* No. C 06-02820, 2007 WL 661914, at *2 (N.D. Cal. Feb. 28, 2007).

III. Plaintiffs are not required to prove general causation (or anything else) at the pleadings stage.

Defendant's proposal insinuates, incorrectly, that Plaintiffs must provide admissible scientific evidence of general causation at the pleadings stage. Leaping from one incorrect assertion to another, the proposal feigns premature concern that Plaintiffs can never prove general causation because the complaints supposedly lack "a reliable scientific foundation to support general causation." *See, e.g.*, ECF No. 61, PageID #: 649. As Defendant well knows, the possibility that cases may fail for lack of general causation exists at the outset of every centralized mass tort. This MDL is not unique in that way. But the outset of an MDL is not the appropriate time to hold

plaintiffs to any standard of proof regarding general causation beyond the *Iqbal/Twombly* notice-pleading standard.

That the complaint may not prove general causation with admissible scientific evidence is not "a compelling and urgent reason to resolve the issue of general causation as expeditiously as possible." *Id*. at PageID#: 659. To the contrary, [h]ypertechnical arguments regarding the allegations" in a complaint represent "an inaccurate understanding of notice pleading." *Jackson*, 842 F.3d at 909. Plaintiffs need not prove anything at the pleading stage, including causation. A complaint must only "provide enough factual support to 'raise a right to relief above the speculative level.'" *Ellison v. General Iron Indus., Inc.*, No. 16C7428, 2016 WL 5934099, at *3 (N.D. Ill. Oct. 12, 2016) (quoting *Twombly*, 550 U.S. at 555).

Plaintiffs' only obligation with respect to general causation now is to plausibly allege that Suboxone film can cause dental injuries under the *Iqbal-Twombly* notice-pleading standard. This is not a high bar, and, as discussed, Plaintiffs provided ample allegations and scientific support to plausibly conclude that Suboxone film causes tooth decay. *See, e.g.*, *Jackson*, 842 F.3d at 908 (holding that the plaintiffs adequately plead proximate cause under Tennessee law by identifying various defects in defendant's car that could have caused the accident and plaintiff's injuries); *Kulich v. Royal Caribbean Group*, No. 21-21215, 2021 WL 7082995, at *9 (S.D. Fla. Sep. 3, 2021) (holding that the complaint met the notice pleading standard even where the plaintiffs did not plead a differential diagnosis); *Benefield v. Pfizer Inc.*, 103 F. Supp. 3d 449, 460 (S.D.N.Y. 2015) (plaintiffs adequately pled medical causation that the

drug caused her injuries where plaintiff pleaded a temporal connection and there was no alternative explanation); *Lee v. Mylan Inc.*, 806 F. Supp. 2d 1320, 1323 (M.D. Ga. 2011) (temporal connection between taking the drug and suffering injury combined with absence of another "obvious alternative explanation" was a plausible explanation sufficient to plead causation under the *Iqbal/Twombly* notice standard).

Plaintiffs concede that "general causation must be determined at some point," but disagree that Defendant's proposed phased discovery is an appropriate, let alone efficient, solution. Defendant's proposal puts too much weight on notice pleading; weight that is reserved for summary judgment at the earliest. *Jackson*, 842 F.3d at 908 ("causal weaknesses will more often be fodder for a summary-judgment motion under Rule 56 than a motion to dismiss under Rule 12(b)(6)"). *See also Benefield v. Pfizer Inc.*, 103 F. Supp. 3d 449, 460 (S.D.N.Y. 2015) (noting that causation allegations must merely be plausible and that any argument otherwise "is premature and appropriately raised on summary judgment or at trial"). Plaintiffs' failure, in Defendant's eyes, to provide a reliable foundation for a scientific opinion in the various complaints has little bearing on whether Plaintiffs *will* provide sufficient general-causation evidence when due; that is, at summary judgment or later. Unless and until Defendant formally asks the Court to consider the *plausibility* of the pleadings with respect to general causation in a dispositive motion, any backdoor attempt by Defendant to do so in its proposal should be ignored.

CONCLUSION

The PLC requests that the Court reject Defendant Indivior's Proposal for Phased Discovery on General Causation and permit discovery on general and specific

causation to proceed on the same course. This will ensure that this MDL proceeds with the just efficiency intended by 28 U.S.C. § 1407.

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Respectfully submitted,

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