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August 28, 2024

VIA ECF
Hon. Karen S. Marston
James A. Byrne U.S. Courthouse
601 Market Street
Philadelphia, PA 19106

Re: In re Glucagon-Like Peptide Receptor Agonists (GLP-1RAS) Prods. Liab. Litig., MDL No. 3094

Dear Judge Marston:

Pursuant to the Court's instructions at the August 2, 2024 Status Conference and Case Management Order No. 18 (Dkt. 235), Plaintiffs respectfully provide this letter brief concerning the Bradford Hill criteria and "how the Hill factors influence the Court's consideration of whether general causation is in fact 'cross cutting' or instead, is more appropriately addressed on an individual Plaintiff by individual Plaintiff basis." Dkt. 235, at 11. In short, Plaintiffs do not dispute that issues of general causation may be cross cutting. Plaintiffs' argument has been and continues to be that general causation should be litigated with a full and complete evidentiary record. The *Suboxone* decision, through its discussion of the Bradford Hill criteria, underscores the significance of the discovery needed to fully and fairly litigate issues of general causation. Therefore, while Plaintiffs reiterate their objections to the early litigation of issues of general causation, as being inefficient, the purpose of this brief is to underscore the need for fulsome discovery across all issues in order to litigate general causation.

The *Suboxone* court explained, in rejecting the defendants' request to bifurcate discovery on general causation from individual plaintiff discovery, that "information germane to general causation will likely go beyond the [investigational new drug applications], [new drug applications], clinical trials, and pharmacovigilance documents that Defendants seek to frontload and might well make additional research, data, or other information Defendants have relevant … Considerably more information than Defendants suggest will likely bear on general causation.[1]

The same is true here. The sources of information relevant to general causation are multifaceted, and investigation of each of the Hill factors requires a fulsome record, including, for example, not only documents relating to Defendants' own clinical trials and testing of these drugs, drafts of study designs, and study data, but also any efforts that Defendants made to monitor and investigate adverse events associated with the drugs (pharmacovigilance), documents reflecting Defendants' knowledge of individual injuries reported to Defendants, to the FDA, or published in the scientific literature or elsewhere. Indeed, Hill factor analysis may require the introduction of limited plaintiff-specific information for full analysis.

[1] *In re Suboxone Film Prods. Liab. Litig.*, 2024 WL 3157608, at *3 (N.D. Ohio June 24, 2024).

The Bradford Hill factors will require discovery into both Defendants' investigation and knowledge of the risks of its GLP-1 RA drugs, necessarily involving a wide array of custodians and functions at each company, and, for many factors, a consideration of individual plaintiffs' specific history and facts. The first category of discovery – into Defendants' knowledge of the dangers of these drugs and what injuries the drugs can cause.[2] Similarly, discovery into Defendants' conduct, internal admissions and attempts to influence the scientific community[3] are all relevant to general causation, and the general causation evidence.

The Bradford Hill causation analysis is one of a multitude of ways to determine causation. It is a framework for analysis that has been widely accepted in the medical and scientific community for evaluating whether a disease or injury can be causally attributed to an exposure. It is a general causation methodology. It is not a case specific causation methodology, although of course a conclusion that an exposure can cause a disease/injury is a necessary cornerstone of any case specific analysis. (And, the strength of the conclusion that a Hill analysis yields can impact a physician's case specific analysis.) Plaintiffs' counsel believe that this methodology will be employed by experts evaluating causation. Those evaluations have not yet occurred and it would be *impossible* for it to reliably take place until those experts have the necessary evidence. At this stage of the litigation, although publicly available evidence amply demonstrates that these drugs do indeed cause the injuries that Plaintiffs allege, a full expert evaluation here would require consideration of evidence to which only Defendants have access. This evidence may or may not materially impact any expert's evaluation of causation, but it needs to be considered. Some basic and obvious examples to anyone who has ever been involved in the evaluation of causation evidence are: the full clinical trial evidence, full pre-clinical evidence, internal causation analyses and internal individual event causation analysis. Clinical trial evidence is deep and broad and *far exceeds* what defendants choose to write up in clinical study reports ("CSRs"), let alone what they publish which is often if not always at variance in some way from the trial findings. And company internal meta-analysis of RCT data is sometime belied by the SAS data itself. Pre-clinical evidence (animal models and *in vitro* experiments) must be disclosed in full and, as is almost always the case, experts need opportunity to personally review tissue slides from the relevant organ systems of the sacrificed animals or re-cuts of the slides. In some litigations, thousands of slides revealing critical signals ignored by the pharmaceutical companies are reviewed. The notion that pharmaceutical companies always have fidelity to scientific principles and evaluation is not only naïve but has been *proven* again and again to be false. Similarly, disproportionality analysis surely were done by these companies and must be disclosed and evaluated; and if they were not done, then the question is begged why not? If they were done, they are one piece of the general causation analysis (and a far more critical piece of the preemption and warning adequacy investigations that

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[2] *See In re Tylenol*, 144 F. Supp. 3d 699, 720 (E.D. Pa. 2015) (discussing elements of failure-to-warn claim); *Runner v, C.R. Bard*, 108 F. Supp. 3d 261, 271 (E.D. Pa. 2015) (same).

[3] *See Merck v. Albrecht*, 587 U.S. 299, 314 (2019) ("[S]howing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that it ***fully informed the FDA of the justifications for the warning*** required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning.") (emphasis added); *Wyeth v, Levine*, 555 U.S. 555, 570 (2009) ("…Wyeth could have analyzed the accumulating data…"); *see also In re Avandia*, 945 F.3d 749, 758 (3d Cir. 2019).

must occur here.) Similarly, the company's evaluation and conclusions regarding AERs (adverse event reports) from both the clinical trials and their post-marketing PV (pharmacovigilance) process must be considered by experts (and perhaps the Court as well: if defendants themselves evaluated individual cases in the very same way that plaintiffs' experts evaluate individual cases does that not cut to the heart of any defense counsel claims that plaintiffs' experts' methodology is unreliable?). Because defendants are, remarkably, denying general causation, those within the company who have been responsible for the medical and scientific issues must be questioned and confronted to investigate why it is that they have rejected causation. Such investigation often yields admissions that both experts and the Court need to consider.

The above outlined information goes directly to evidence called for by a Bradford Hill analysis. The important Bradford Hill *Consistency* factor asks whether different lines of evidence support a causation conclusion; lines of evidence *means* clinical trials, animal evidence, bench research, case reports and more. The *Biologic Plausibility* analysis is based in part on animal and *in vitro* experiments. *Biologic Gradient* (dose response) is often revealed in the clinical trial results regarding adverse events; indeed, we see public evidence that there seems to be a dose response relationship for gastrointestinal adverse events and drop-outs but the full evidence including the SAS data should be provided. The clinical trial results certainly add to the *Strength of the Association* factor and the trials themselves are in fact experiments thus providing evidence under the Hill questions regarding experimental evidence. Critically, under Hill, is the challenge, de-challenge (with or without re-challenge) evidence and this is often found in adverse events reported to the company. What the defendants found in any studies that they conducted in drugs of the same class is always important to experts considering causation issues. It not only is relevant to the Hill *Analogy* factor but also the *Strength of the Association* factor.

As mentioned above, expert discovery should occur after the parties have conducted the requisite and significant fact discovery. As the *Suboxone* court held, after a meticulous assessment of the Hill factors, "[R]eliable opinions on general causation will likely be sufficiently bound up with matters that make discretely sequencing discovery in this MDL exceedingly difficult."[4] The *Suboxone* court noted, "the Hill criteria contemplate broad consideration of all relevant facts and data."[5] Similarly, as Judge Chhabria put it in the *Roundup* MDL, "[T]he Bradford Hill framework asks experts to survey ***all the available evidence*** that might support or disprove causation."[6] Courts assessing causation using the Hill criteria have found that they cannot be used "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,"[7] or "artificially divorced from ***the entirety of the scientific record***" bearing on causation.[8]

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[4] *Suboxone*, 2024 WL 3157608, at *3.
[5] *Suboxone*, 2024 WL 3157608, at *3.
[6] *In re Roundup*, 390 F. Supp. 3d 1102, 1130 (N.D. Cal. 2018), *aff'd sub nom. Hardeman v, Monsanto*, 997 F.3d 941 (9th Cir. 2021) (emphasis added).
[7] *Suboxone*, 2024 WL 3157608, at *3.
[8] *See Henderson v, Lockheed Martin*, 2023 WL 11108737, at *9 (M.D. Fla. Sept. 18, 2023).

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In this case, the significant amount of discovery required to litigate general causation for each of the Defendants' drugs and each of the Plaintiffs' injuries removes any efficiencies gained by litigating "cross cutting" general causation issues. However, should the Court decide that general causation should be litigated outside of a bellwether context, Plaintiffs request the full record fairness requires.

Respectfully,

/s/ Paul Pennock
Paul Pennock
MORGAN & MORGAN
350 Fifth Avenue, Suite 6705
New York, NY 10118
Telephone: (212) 738-6299
Email: ppennock@forthepeople.com

/s/ Parvin K. Aminolroaya
Parvin K. Aminolroaya
SEEGER WEISS LLP
55 Challenger Rd., 6th Floor
Ridgefield Park, NJ 07660
Telephone: (973) 639-9100
Email:paminolroaya@seegerweiss.com

/s/ Jonathan Orent
Jonathan Orent
MOTLEY RICE LLC
40 Westminster St., 5th Floor
Providence, RI 02903
Telephone: (401) 457-7700
Email: jorent@motleyrice.com

/s/ Sarah Ruane
Sarah Ruane
WAGSTAFF & CARTMELL

[9] *Suboxone*, 2024 WL 3157608, at *3.

4740 Grand Avenue Suite 300
Kansas City, MO 64112
Telephone: (816) 701-1123
Email: sruane@wcllp.com

Co-Lead Counsel

Cc: Defense Counsel of Record
Bobbie Liebenberg
Nina Spizer