IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

IN RE: TEPEZZA MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	No. 1:23−cv−03568 MDL No. 3079
This Document Relates to Member Cases: No. 1:22-cv-06562 (*Pledger*) No. 1:23-cv-02503 (*Polanco*) No. 1:23-cv-02659 (*Stern*) No. 1:23-cv-02703 (*Ford*) No. 1:23-cv-03033 (*Chryssos*) No. 1:23-cv-03575 (*Kanesta-Rychner*) No. 1:23-cv-03585 (*Meyers*) No. 1:23-cv-15306 (*Egger*) No. 1:23-cv-15994 (*Perkett*)	Judge Thomas M. Durkin Magistrate Judge M. David Weisman

DEFENDANT HORIZON THERAPEUTICS USA, INC.'S MEMORANDUM IN SUPPORT OF ITS MOTION TO DISMISS NINE INITIAL BELLWETHER DISCOVERY COMPLAINTS PURSUANT TO FED. R. CIV. P. 12(b)(6)

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Horizon Therapeutics USA, Inc. ("Horizon") moves this Court to dismiss the First Amended Complaints ("FACs") of nine Initial Bellwether Discovery cases based on Federal Preemption.[1] Plaintiffs' FACs do not allege sufficient facts to state a plausible claim for relief. *See* Fed. R. Civ. P. 8(a); Fed. R. Civ. P. 12(b)(6); *Ashcroft v. Iqbal*, 556 U.S. 662 (2009); *Bell Atl. Corp. v. Twombly*, 550 U.S. 544 (2007). Plaintiffs' claims are all premised upon a failure to warn involving the labeling approved by the United States Food and Drug Administration ("FDA") for Horizon's biologic medicine, Tepezza®. As shown below, these claims are preempted as pleaded.

The FDA approved Tepezza®, including its label, in January 2020 knowing that hearing impairment was an adverse reaction observed in Horizon's pivotal clinical trials. With this approval, Tepezza® became the first and only medication specifically indicated for thyroid eye disease ("TED"), a disease that results in proptosis or exophthalmos (wherein the eyes push forward and bulge from the eye sockets), eyelid and eye redness or "bloody eyes", and immense pain. Upon approval, FDA heralded Tepezza® as "an important milestone" for the treatment of TED with the "potential to alter the course of the disease, potentially sparing patients from needing multiple invasive surgeries."[2] The "Highlights of Prescribing Information" section on the first page

[1] Horizon moves to dismiss nine of the twelve Initial Bellwether Discovery cases for the reasons set forth in this motion, as indicated in the caption. Horizon does not seek dismissal by this motion of three Initial Bellwether Discovery cases because they present different factual allegations: *Merriweather v. Horizon Therapeutics USA, Inc.*, No. 1:23-cv-02714 (N.D. Ill. filed May 1, 2023); *Meilleur. Horizon Therapeutics USA, Inc.*, No. 1:23-cv-15501 (N.D. Ill. filed Oct. 31, 2023); and *Bounds v. Horizon Therapeutics USA, Inc.*, No. 1:23-cv-06423 (N.D. Ill. filed Aug. 29, 2023).

[2] *See* News Release, *FDA approves first treatment for thyroid eye disease*, U.S. FOOD & DRUG ADMIN. (Jan. 21, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-thyroid-eye-disease (last visited July 17, 2024) (**Exhibit L**). *See also* Horizon's concurrently filed Request for Judicial Notice, asking the court to take judicial notice this Exhibit L, other FDA documents and websites, and press release that are referenced herein and in the FACs. The Supreme Court has instructed that when deciding a motion to dismiss, "courts must consider the complaint in its entirety, as well as other sources courts ordinarily examine when ruling on Rule 12(b)(6) motions to dismiss, in particular, documents incorporated into the complaint by reference, and matters of which a court may take judicial notice." *Tellabs, Inc. v. Makor Issues & Rts., Ltd.*, 551 U.S. 308, 322 (2007): *Jackson v. Kane Cnty,*, No. 09 C 4154, 2010 WL 4719713, at *2 n.2 (N.D. Ill. Nov. 9, 2010) ("In ruling on a 12(b)(6) motion to dismiss,

of the January 2020 label listed "hearing impairment" as one of the "[m]ost common adverse reactions." The "Clinical Trials Experience" section of the label also included information about reports of hearing impairment, including "deafness."

The nine Initial Bellwether Discovery plaintiffs subject to this Motion all allege they completed their prescribed Tepezza® treatment prior to September 30, 2022. Plaintiffs claim that Horizon failed to change its FDA-approved label to adequately warn their physicians of hearing-related adverse events before they were prescribed Tepezza®.

The Supreme Court has held that failure-to-warn claims based on FDA-approved labeling are preempted when there is no applicable regulation permitting a manufacturer to unilaterally change its label—i.e., without FDA approval. *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) (citing the "changes being effected" regulation applicable to drugs, 21 C.F.R. § 314.70(c)(6)(iii)). The "changes being effected" ("CBE") regulation is the sole regulation that permits such a change *only if* the requested change is based on "newly acquired information" not previously provided to the FDA. *Id.* at 568. The "changes being effected" regulation for biologics like Tepezza®—which mirrors the regulation discussed in *Wyeth*—mandates that "newly acquired information" must "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 601.12(f)(2).

To plausibly state a non-preempted claim, plaintiffs must offer specific allegations of "newly acquired information" that Horizon obtained after FDA approved Tepezza® and before plaintiffs' last use. *In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 42 (1st Cir. 2015); *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019). Plaintiffs' FACs

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the court may take judicial notice of matters of public records.") (citing *Cancer Found., Inc. v. Cerberus Cap. Mgmt.*, 559 F.3d 671, 675 n.2 (7th Cir. 2009)); *see also* Fed. R. Evid. 201(b).

fail to allege any such "newly acquired information" that "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA" prior to their alleged final use of Tepezza® (i.e., from the time of FDA's approval of Tepezza® in January 2020 to before the final infusion of the nine plaintiffs on September 30, 2022).

Despite plaintiffs' allegation that "new" information arose after FDA approved Tepezza® but before plaintiffs completed their Tepezza® treatments, plaintiffs fail to allege that such "new" information establishes, or allows the Court to infer, that Horizon was aware of a change in the severity of hearing impairment. Nor do plaintiffs allege that Horizon was aware of any "new" information that established a change in the frequency of hearing impairment. Accordingly, the FACs fail to allege "newly acquired information" as required by the regulation and must be dismissed as preempted.

BACKGROUND

I. Federal Regulation of Biologic License Applications

To obtain FDA approval for a new biologic product, a manufacturer must submit a Biologic License Application ("BLA") that includes, among other things, data from nonclinical laboratory and clinical studies demonstrating that the product meets prescribed requirements for safety and a proposed label setting out the conditions under which the drug is intended to be used. 21 U.S.C. § 355(b); 42 U.S.C. § 262(a); 21 C.F.R. §§ 601.2(a), 600.3(kk). FDA's premarket approval of a BLA includes the approval of the exact text of the initial product labeling. *See* 21 C.F.R. §§ 601.2(a), 601.12. The FDA reviews the proposed label to determine whether it is "false or misleading." 21 C.F.R. §§ 201.56, 201.57. Once the application is approved, the "manufacturer must distribute the drug using the FDA-approved label. Otherwise, the drug is misbranded and may not be distributed." *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 806 (7th Cir. 2018).

It is common knowledge that all prescription drugs carry some risk, making the label an integral part of FDA's review and approval process. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (when approving drugs, FDA conducts a cost-benefit analysis that balances the potential benefits of the drug against the risk of harm). Accordingly, Congress delegated to FDA responsibility for undertaking the careful balancing process necessary to determine which prescription drugs (all of which are recognized to be highly dangerous to at least some patients) are sufficiently safe and effective to warrant their availability for specific indications on a prescription basis. *See Weinberger v. Bentex Pharms. Inc.*, 412 U.S. 645, 654 (1973) (finding that the court's referral to FDA concerning whether a drug is safe and effective was appropriate); *id.* (collecting cases demonstrating that where a court lacks technical expertise, the congressionally created agency charged with "regulating the subject matter" should be given deference).

FDA closely regulates post-approval changes to FDA-approved biologics' labeling. Regulations significantly limit a manufacturer's ability to make unilateral labeling changes without FDA's prior approval. *See* 21 U.S.C. § 355(o)(4). "Indeed, permitting a sponsor to unilaterally rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated." *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008) (**Exhibit B**). As such, "[a]lthough CBE supplements permit sponsors to implement labeling changes before FDA approval of the change, FDA views a CBE supplement as a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product." *Id.*

FDA-approved labeling generally preempts state law failure to warn claims because "a manufacturer may only change a drug label after FDA approves a supplemental application." *Wyeth*, 555 U.S. at 568 (citing 21 C.F.R. § 314.70(c)(6)(iii)). The Supreme Court has recognized that the "changes being effected" regulation is the only exception and "permits a manufacturer to make certain changes to its label before receiving the agency's approval" based on "newly acquired information" not previously provided to FDA. *Id*. "Newly acquired information" is defined by the regulations as:

> [D]ata, analyses, or other information not previously submitted to the [FDA] which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 601.12(f)(6). The CBE procedure, therefore, is only available to make changes based on "newly acquired information" about new risks or about a change in the appreciation of a known risk discovered after FDA approves a but before plaintiffs' exposure. *Id.*[3] *In re Celexa & Lexapro*,

[3] *R.S.B. v. Merck & Co.*, No. 20-C-1402, 2021 WL 6128161, at *3 (E.D. Wis. Dec. 28, 2021) (relevant time period is between label approval and plaintiff's last use); *Ideus v. Teva Pharms. USA, Inc.*, No. 4:16-CV-3086, 2017 WL 6389630, at *3 (D. Neb. Dec. 12, 2017) (identifying the relevant time period as after label approval but before exposure); *see also Mahnke v. Bayer Corp.*, No. 2:19-CV-072171-RGK-MAA, 2019 WL 8621437, at *3–4 (C.D. Cal. Dec. 10, 2019) (review paper published after plaintiff's exposure was "insufficient to show that [defendant] could have invoked the CBE regulation"); *Sabol v. Bayer Healthcare Pharm., Inc.*, 439 F. Supp. 3d 131, 148 n.13 (S.D.N.Y. 2020) ("The Court will disregard the many articles cited in the Amended Complaint that were published after [plaintiff's] last [use of the product]. These studies can have no bearing on her failure-to-warn claim."); *Ridings v. Maurice*, 444 F. Supp. 3d 973, 993 (W.D. Mo. 2020) ("[S]tudies published after a plaintiff's injury [are not] relevant to constitute newly acquired information."); *Rayes v. Novartis Pharms. Corp.*, No. 21-55723, 2022 WL 822195 *2 (9th Cir. Mar. 18, 2022) ("[D]istrict court properly disregarded the complaint's allegations of post-marketing adverse event reports that post-dated [plaintiff's] final injection of [drug]"); *Silver v. Bayer Healthcare Pharm., Inc.*, No. 2:19-cv-3495-DCN-MHC, 2021 WL 4472857, *9 (D.S.C. Sept. 30, 2021) ("Silver must allege that new information arose sometime after March 2015—when the FDA last approved Eovist's label—and December 2016—when Silver was injected with Eovist."); *Goodell v. Bayer Healthcare Pharm., Inc.*, No. 18-cv-10694-IT, 2019 WL 4771136 (D. Mass. Sept. 30, 2019) ("*Celexa* thus requires Plaintiff to provide plausible allegations of 'newly acquired information' that manifested after the FDA's approval of the Magnevist label but before Plaintiff's injury.").

779 F.3d at 42 (affirming dismissal because complaint contained no allegations that allowed the court to infer the existence of "newly acquired information"); *Gibbons*, 919 F.3d at 708 ("[T]o state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead 'a labeling deficiency that [Defendants] could have corrected using the CBE [Changes Being Effected] regulation.'").

II. Plaintiffs' Allegations

FDA approved the Tepezza® BLA, including the product labeling, in January 2020. FAC ¶ 42, *Chryssos v. Horizon Therapeutics USA, Inc.,* No. 1:23-cv-03033 (N.D. Ill. Feb. 29, 2024), ECF No. 12 (**Exhibit A**).[4] Tepezza® is the first and only FDA-approved treatment for TED, a disease "characterized by progressive inflammation in the tissues around the eyes." *Id.* ¶ 28. Inflammation causes proptosis or exophthalmos (wherein the eyes push forward and bulge from the eye sockets), eyelid and eye redness or "bloody eyes," and immense pain. *Id.* ¶¶ 28, 31. TED may also cause: eyelid retraction (wherein patients cannot fully shut their eyelids); dry eyes; eye pain, difficulty, or an inability to look around; impaired vision, including blurred or double vision (diplopia); eye misalignment or strabismus (wherein the two eyes point in different directions); inflamed white area of eye; excessive eye watering or tearing; an intolerance to bright lights; and eyelid swelling. *See id.* Prior to Tepezza®'s approval, TED was treated using corticosteroids and surgery in "moderate-to-severe disease." *Id.* ¶ 34–35. There was no FDA-approved medicine to treat TED.

The FDA-approved label issued at product launch in January 2020, listed on the first page of the label in the "Highlights of Prescribing Information," hearing impairment as one of the

[4] Horizon refers to the FAC in *Chryssos*, No. 1:23-cv-03033 (N.D. Ill. Feb. 29, 2024), ECF No. 12 (**Exhibit A**). While the exact citation may vary among the cases, the allegations set forth in the *Chryssos* FAC are representative of the nine Initial Bellwether Discovery cases subject to this motion.

"[m]ost common adverse reactions." 2020 Tepezza® Label at 1 (**Exhibit C**).[5] The "Clinical Trials Experience" section of the 2020 Tepezza® Label also informed prescribers about reports of hearing impairment (including "deafness") during clinical trials in the "Adverse Reactions" section of the label. *Id.* ¶ 6.1; FAC ¶¶ 52, 67.

In January 2023, following receipt of a limited number of post-approval hearing-related adverse event reports, Horizon submitted a supplemental biologics license application (sBLA) to FDA seeking to strengthen the "Warnings and Precautions" section of the Tepezza® label. FAC ¶ 118. The sBLA sought the addition of a "Warnings and Precautions" addressing "severe hearing impairment including hearing loss, which in some cases may be permanent." FAC ¶ 140. FDA approved Horizon's sBLA in July 2023. *See* **Exhibit D** ("2023 Tepezza® Label").[6] Plaintiffs do not allege that Horizon sought to strengthen the label due to an increase in the frequency of hearing impairment adverse event reports.

The nine Initial Bellwether Discovery plaintiffs subject to this Motion allege they were prescribed and exposed to Tepezza® between April 2020 and September 2022. Specifically, the alleged final infusion date for the nine Initial Bellwether Discovery plaintiffs subject to this Motion is as follows:

Bellwether Discovery Case	Alleged Initial Infusion Date	Alleged Final Infusion Date	FAC ¶
Meyers, 1:23-cv-03585 (ECF No. 6)	4/2020	9/30/2020*	10
Stern, 1:23-cv-02659 (ECF No. 14)	5/2021	10/31/2021*	10
Ford, 1:23-cv-02703 (ECF No. 11)	8/2021	10/31/2021*	10

[5] *Drug Label for Tepezza®*, U.S Food & Drug Admin. (Jan. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761143Orig1s000lbl.pdf (**Exhibit C**).

[6] *See Drug Label for Tepezza®*, U.S Food & Drug Admin. (July 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761143s023lbl.pdf (**Exhibit D**). The Tepezza® label continues to include hearing impairment in the "Clinical Trials Experience" section of the FDA-approved Tepezza® Label. The 2023 Tepezza® Label was also amended to include references to tinnitus and deafness neurosensory.

Pledger, 1:22-cv-06562 (ECF No. 36)	6/2021	12/31/2021*	10
Polanco, 1:23-cv-02503 (ECF No. 10)	11/2021	5/31/2022*	10
Egger, 1:23-cv-15306 (ECF No. 3)	3/2022	8/31/2022*	10
Kanesta-Rychner, 1:23-cv-03575 (ECF No. 15)	4/27/2022	9/28/2022	10
Chryssos, 1:23-cv-03033 (ECF No. 12)	6/2022	9/30/2022*	10
Perkett, 1:23-cv-15994 (ECF No. 6)	4/11/2022	9/19/2022	10
* Plaintiff alleges that his/her final exposure occurred "through" the identified month, without identifying a specific date. To be conservative, Horizon assumes for the purpose of motions practice that the infusion occurred on the last day of the identified month.			

All nine Initial Bellwether Discovery plaintiffs at issue in this Motion allege they subsequently developed "permanent hearing loss" and/or "tinnitus." FAC ¶ 12. Despite the language in the 2020 Tepezza® Label about reports of such hearing loss (including "deafness"), plaintiffs allege that Horizon failed to adequately warn of "the serious risk of permanent hearing loss and/or tinnitus" in patients taking Tepezza®. *See* **Exhibit C** at 1, ¶ 6.1; FAC ¶ 11. Plaintiffs assert causes of action for strict liability, negligence, design defect, and fraudulent misrepresentation, all grounded in a failure-to-warn theory.[7]

Many of plaintiffs' allegations of information known to Horizon address irrelevant information about Tepezza® that post-dates their alleged exposures. For example, plaintiff *Meyers* alleges final exposure to Tepezza® in September 2020, FAC ¶ 10, just eight months after FDA approval. *Meyers'* FAC, however, includes twenty-three paragraphs regarding facts that allegedly occurred after her final exposure to Tepezza®. *See* FAC ¶¶ 55–59, 77, 79, 81, 99, 100–01, 105, 107–13, 115–17. According to *Meyers'* FAC, prior to her final infusion, only twenty-five hearing-related adverse events had been observed and reported to FDA, FAC ¶ 77(a)–(x), a single article had been published about the pivotal clinical trials prior to *Meyers'* final exposure was available,

[7] Bellwether plaintiff Kanesta-Rychner asserts claims only for strict liability grounded in a failure-to-warn theory. *See Kanesta-Rychner*, Civ. No. 1:23-cv-03575, ECF Nos. 15, 17. Bellwether plaintiff Ford does not assert a claim for strict liability. *See Ford*, Civ. No. 1:23-cv-03575, ECF Nos. 11, 13.

id. ¶ 99(a), and the alleged results of Horizon's compassionate use program (i.e., "Study 401 EAP") were finalized, *id.* ¶ 120. Plaintiffs do not allege that *any* of these reports or publications constitutes a risk of a different type of or an increase in severity or frequency of the adverse event at issue. As shown below, none of the plaintiffs allege that information became known to Horizon that satisfies the requirements of 21 C.F.R. § 601.12(f).

ARGUMENT

I. Legal Standard

Federal Rule of Civil Procedure 8 requires "a short and plain statement of the claim showing that the pleader is entitled to relief." The Rule "contemplates the statement of circumstances, occurrences, and events in support of the claim presented" and does not authorize a plaintiff's "bare averment that he wants relief and is entitled to it." *Twombly*, 550 U.S. at 555 n.3. "[M]ore than labels and conclusions" are required "and a formulaic recitation of the elements of a cause of action will not do." *Id.* at 555 (internal citations omitted); *see also Iqbal*, 556 U.S. at 681. "[T]he pleading standard Rule 8 announces does not require 'detailed factual allegations,' but it demands more than an unadorned, the-defendant-unlawfully-harmed-me accusation." *Iqbal*, 556 U.S. at 678 (internal citations omitted). A complaint is insufficient under Rule 12 where it does not contain sufficient factual allegations to "state a claim to relief that is plausible on its face." *Twombly*, 550 U.S. at 570.

The Supreme Court of the United States has issued three decisions clarifying the test for preemption in cases involving failure-to-warn claims made against pharmaceutical manufacturers: *Wyeth v. Levine*, 555 U.S. 555 (2009); *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011); and *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). The Supreme Court held that to avoid preemption, a plaintiff must demonstrate that a manufacturer "could *independently* do under federal law what state law requires of it." *Mensing*, 564 U.S. at 620 (quoting *Wyeth*, 555 U.S., at

573 (finding no pre-emption where the defendant could 'unilaterally' do what state law required). The Supreme Court also held that preemption is a question of law and "one for a judge to decide, not a jury." *Albrecht*, 139 S. Ct. at 1672; *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 390, 393–96 (7th Cir. 2010) (referring to preemption issue as "a legal one" and analyzing preemption as a matter of law).[8]

The Supreme Court further made clear that a failure to warn claim based on FDA-approved labeling is preempted absent an applicable regulation allowing a manufacture to independently—i.e., unilaterally—change its label. *Wyeth*, 555 U.S. at 568 (citing 21 C.F.R. § 314.70(c)(6)(iii)). There is a single, narrow regulation that potentially allows a manufacturer to unilaterally change its label. The "changes being effected" regulation provides that a manufacturer may unilaterally change a label *only if* the requested change is based on "newly acquired information" that "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 601.12(f)(2) ("changes being effected" regulation applicable to biologics); *Wyeth*, 555 U.S. at 568; *Albrecht*, 139 S. Ct. at 1682 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

Therefore, in the context of a state-law-based failure-to-warn claim, to plausibly give rise to a claim that is not preempted, plaintiffs must plead sufficient factual content to allow "the court to draw the reasonable inference," *Iqbal*, 556 U.S. at 678, that there was information "not previously submitted to the [FDA]" that "reveal[ed] risks of a different type or greater severity or frequency than previously included in submissions to FDA" and that also demonstrates "reasonable evidence of a causal association with a drug." 21 C.F.R. § 601.12(f)(6); *see also, e.g., In re Celexa & Lexapro*, 779 F.3d at 42 (affirming dismissal because complaint contained no

[8] In *Albrecht*, the Supreme Court held "that a judge, not the jury, must decide the preemption question." 139 S. Ct. at 1679–80; *see also Guilbeau v. Pfizer, Inc.*, 880 F.3d 302, 318 (7th Cir. 2018) ("preemption is a legal question for determination by the courts….").

allegations that allowed the court to infer the existence of "newly acquired information"); *Gibbons*, 919 F.3d at 708 ("[T]o state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead 'a labeling deficiency that [Defendants] could have corrected using the CBE [Changes Being Effected] regulation.'").

II. Plaintiffs' FACs Fail to Allege "Newly Acquired Information" That Would Trigger the Changes Being Effected ("CBE") Exception to Preemption

Following the Supreme Court's holdings in *Wyeth*, *Mensing*, and *Albrecht*, five United States Courts of Appeals, including the Seventh Circuit, have concluded that failure-to-warn claims regarding FDA-approved product are preempted unless plaintiffs can establish the existence of "newly acquired information" that would have supported a unilateral label change under the CBE regulation prior to plaintiffs' last exposure to the medicine. *Dolin*, 901 F.3d at 806 (state law claim "is preempted if [manufacturer] could not have added" warning using the CBE regulation); *In re Celexa & Lexapro*, 779 F.3d at 41 (affirming dismissal because complaint contained no allegations of "newly acquired information"); *Gibbons*, 919 F.3d at 708 ("[T]o state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead 'a labeling deficiency that [Defendants] could have corrected using the CBE [Changes Being Effected] regulation.'"); *Gayle v. Pfizer Inc.*, 452 F.Supp. 3d 78, 87–88 (S.D.N.Y. 2020), *aff'd*, 847 F. App'x 79 (2d Cir. 2021) (summary order affirming grant of motion to dismiss for failure to adequately plead newly acquired information); *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329, 337 (4th Cir. 2021) (state law challenge to FDA-approved warnings can "proceed only when the defendant had the unilateral ability to change that labeling; otherwise, the claim is preempted."); *Hickey v. Hospira*, 102 F.4th 748, 759 (5th Cir. 2024) (holding that "the availability of the CBE regulation is a threshold issue" and that the "district court erred by failing to enforce the requirement that

newly acquired information must 'reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA'").

Moreover, because plaintiffs must make such a showing at the pleading stage, courts have granted motions to dismiss where plaintiffs failed to allege the existence of "newly acquired information." The First Circuit held that "a necessary step in defeating" a pleading-stage "preemption defense is to establish that the complaint alleges a labeling deficiency that [the defendant] could have corrected using the CBE regulation." *In re Celexa & Lexapro*, 779 F.3d at 41. In that case, the First Circuit "scrutinized the complaint" and found that the plaintiffs had failed to allege any "newly acquired information" that was "unknown prior to label approval." *Id.* at 43. The court therefore held that the plaintiffs' complaint could not "plausibly be read" to allege that defendant could independently change its label prior to plaintiff's alleged exposure, affirming dismissal of the complaint. *Id.*

The Second Circuit endorsed this approach in *Gibbons,* requiring a plaintiff to plead "'newly acquired information' to meet the Rule 8 threshold of 'a short and plain statement of the claim showing that the pleader is entitled to relief,'"—*i.e.*, that the defendants could unilaterally change the label pursuant to the CBE regulation without FDA approval. 919 F.3d at 709. Because the plaintiff there failed to "plead a labeling deficiency that Defendants could have corrected using the CBE regulation" by alleging the non-speculative existence of "newly acquired information," it affirmed the granting of a motion to dismiss. *Id.* at 708–09 (internal quotations and alterations omitted). No federal court of appeal has issued a published decision that conflicts with these rulings.[9] Numerous district courts outside the Seventh Circuit have also articulated identical

[9] In *Rayes v. Novartis Pharm. Corp.*, a case also involving a biologic medication, the district court granted the drug manufacturer's motion to dismiss based upon preemption. No. EDCV 21-201 JGB (KKX), 2021 WL 2410677, at *5 (C.D. Cal. June 11, 2021). On appeal, in an unpublished and nonprecedential opinion, the Ninth Circuit affirmed in part and reversed in part. *Rayes v. Novartis Pharms. Corp.*, No. 21-55723,

requirements for properly pleading a state law failure-to-warn claim involving an FDA-approved branded medication.[10]

All nine Initial Bellwether Discovery plaintiffs at issue in this Motion allege exposure to Tepezza® prior to September 30, 2022. *See* FAC ¶ 10, *Chryssos*, 1:23-cv-03033 (ECF No. 12) (latest alleged exposure date of "through September 2022"). The Court should disregard the vast majority of plaintiffs' allegations that post-date the plaintiffs' alleged exposures.[11] Plaintiffs' only allegations of "new" information between the initial January 2020 Label and September 30, 2022, are anecdotal post-market reports of hearing-related ailments, case reports, case series, and publications discussing current treatments for TED.

2022 WL 822195 (9th Cir. Mar. 18, 2022). The Ninth Circuit agreed that a plaintiff must plead the existence of "newly acquired information" in order to satisfy the CBE regulation to avoid preemption. *Id.* at *1. Although the court stated that adverse event reports and "multiple cases" constituted "newly acquired information," *id.*, it did not examine whether this constituted information "not previously submitted to the [FDA]" that "reveal[ed] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 601.12(f)(6).

[10] **First Circuit:** *Goodell v. Bayer Healthcare Pharms.*, No. 18-CV-10694-IT, 2019 WL 4771136 (D. Mass. Sept. 30, 2019). **Second Circuit:** *McGrath v. Bayer Healthcare Pharms., Inc.*, 393 F. Supp. 3d 161, 168-70 (E.D.N.Y. 2019); *Gayle,* 452 F. Supp. 3d at 87-88 (S.D.N.Y. 2020), *aff'd*, 847 F. App'x 79 (2d Cir. 2021) (summary order); *Herlth v. Merck & Co., Inc.*, No. 3:21-cv-438 (JAM), 2022 WL 788669 (D. Conn. Mar. 15, 2022). **Third Circuit:** *Zamfirova, v. Amag Pharms., Inc*., No. 20-CV-00152, 2021 WL 2103287 (D.N.J. May 25, 2021). **Fifth Circuit:** *Smith v. GE Healthcare, Inc.*, No. 3:19-CV-00492, 2020 WL 1880787, at *7 (W.D. La. Mar. 31, 2020), *report and recommendation adopted,* No. 3:19-CV-00492, 2020 WL 1875644 (W.D. La. Apr. 15, 2020); *Thomas v. Bracco Diagnostics, Inc.*, No. 3:19-CV-00493, 2020 WL 1016273, at *9 (W.D. La. Feb. 27, 2020)*, report and recommendation adopted,* No. 3:19-CV-0493, 2020 WL 1243389 (W.D. La. Mar. 13, 2020). **Sixth Circuit:** *Maze v. Bayer Healthcare Pharms, Inc.*, No. 4:18-CV-21-TAV-CHS, 2019 WL 1062387, at *3 (E.D. Tenn. Mar. 6, 2019). **Eighth Circuit:** *Ideus v. Teva Pharms. USA, Inc.*, No. 4:16-CV-3086, 2017 WL 6389630 (D. Neb. Dec. 12, 2017); *Stube v. Pfizer Inc*., 446 F. Supp. 3d 424 (W.D. Ark. 2020). **Ninth Circuit:** *Mahnke v. Bayer Corp.*, No. 2:19-CV-07271-RGK-MAA, 2020 WL 2048622 (C.D. Cal. Mar. 10, 2020); *Drescher v. Bracco Diagnostics, Inc.*, No. CV-19-00096-TUC-RM (LCK), 2020 WL 699878 (D. Ariz. Jan. 31, 2020); *Holley v. Gilead Scis., Inc.*, 379 F. Supp. 3d 809, 827 (N.D. Cal. 2019); *Klein v. Bayer Healthcare Pharms. Inc.*, No. 2:18-CV-01424-APG-EJY, 2019 WL 3945652 (D. Nev. Aug. 21, 2019).

[11] *See* FAC ¶ 81vvv.–kkkk. (adverse event reports that post-date the plaintiffs' alleged exposures), ¶ 84b.–r., bb.–gg. (same), ¶ 85a. (adverse event report that post-date the plaintiffs' alleged exposures); ¶¶ 122-24, ¶¶ 127-129 (case reports that post-date the plaintiffs' alleged exposures).

To make a change under the CBE regulation, the manufacturer must satisfy three requirements. *See In re Celexa & Lexapro*, 779 F.3d at 37. First, the requested change must be based on "newly acquired information" that was "not previously submitted to the Agency." 21 C.F.R. § 601.12(f)(2), (f)(6). Second, it must be based on "newly acquired information" that "reveal[s] risks of a different type or greater severity or frequency." 21 C.F.R. § 601.12(f)(2), (f)(6). Third, the "newly acquired information" must also demonstrate "reasonable evidence of a causal association." 21 C.F.R. § 601.12(f)(2) (referencing 21 C.F.R. § 201.57(c)(6)(i)). Plaintiffs fail to meet these requirements.

A. Plaintiffs do not allege information concerning risks "not previously submitted to the Agency."

Plaintiffs do not allege that any of the material during the relevant time frame—between the January 2020 approval of Tepezza® and plaintiffs' latest alleged infusion date—"reveal[s] risks of a different type . . . than previously included in submissions to FDA."[12] Nor could they. As plaintiffs concede, FDA was aware of reports of hearing impairment, the very injury plaintiffs allege, in patients taking Tepezza® and that information was explicitly included in the initial 2020 Tepezza® Label. *See* FAC ¶¶ 52, 67.[13] FDA was even aware of reports from the clinical trials of hearing-related events, including deafness, that remained unresolved at the time FDA approved

[12] *See id.* ¶¶ 78–86, ¶¶ 99–117; 21 C.F.R § 601.12(f)(6).

[13] Plaintiffs cannot argue that "tinnitus" is a "risk[] of a different type … than previously included in submissions to FDA" because "tinnitus" was observed in in the clinical trials and known to FDA at the time the 2020 Tepezza® Label was initially approved. *See Clinical Review of Tepezza®,* U.S Food & Drug Admin. (Jan. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761143Orig1s000MedR.pdf (**Exhibit E**) (listing cases of tinnitus observed in the clinical trials and discussing tinnitus in the hearing impairment section of "Application Issues"). In acknowledging the tinnitus, and loss of hearing adverse event reports, FDA concluded that hearing impairment would be listed in the "adverse reaction section of the labeling." *Id.* at 61. Tinnitus was later added to the 2023 Tepezza® Label, to provide further clarification of this hearing-related adverse events that was observed in the clinical trial. *See id.* at 54, 61; *see also* **Exhibit C** at § 6.1, Table 1.

Tepezza®.[14]

B. Plaintiffs' alleged adverse event reports and publications do not "reveal risks of a different type or greater severity or frequency."

i) Plaintiffs' alleged adverse event reports are not "information not previously submitted to the [FDA]" nor do plaintiffs allege that they reveal "risks of a different type or greater severity or frequency."

To qualify as "newly acquired information," the alleged information must not have been "previously submitted to the [FDA]." 21 C.F.R § 601.12(f)(6). Here, as plaintiffs allege, the 220 adverse event reports relied upon by plaintiffs were reported and known to the FDA prior to plaintiffs' alleged use of Tepezza®. In fact, plaintiffs allege that *all* of the relevant adverse event reports were submitted to FDA prior to or during each of plaintiffs' final exposures. FAC ¶ 77 (alleging that the adverse event reports were "reported … to the FDA" before or during plaintiffs' treatment); ¶¶ 78 (same), 80 (same), 82 (same). Adverse event reports that were known to FDA cannot constitute newly acquired information. 21 C.F.R § 601.12(f)(6) (defining newly acquired information as "information not previously submitted to [FDA]").

Even if FDA was not aware of these post-marketing adverse event reports, plaintiffs do not allege that this information indicated a greater frequency or severity of the condition at issue—i.e., a change in a risk that FDA was already aware of. The complaints neither claim such an increase in frequency or severity, nor do they allege facts from which the Court could infer one. In fact, without knowing the total number of patients who had taken Tepezza®, it is not possible to

[14] *See* Presentation by Horizon Therapeutics to FDA's Dermatologic and Ophthalmic Drugs Advisory Committee at 71 (noting patients with ongoing deafness and tinnitus), *Teprotumumab for Treatment of Thyroid Eye Disease, U.S Food & Drug Admin.* (Dec. 13, 2019, 8:01 AM to 3:22 PM), https://www.fda.gov/media/133645/download (**Exhibit F**); *see also* Transcript of *December 13, 2019 Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee*, U.S Food & Drug Admin. (Dec. 13, 2019), (**Exhibit G**), at 264:14 to 265:8 (committee members discussing "patients that did no recover" and "a potential for irreversible change in one sense"), https://www.fda.gov/media/135336/download.

determine whether the alleged adverse event reports demonstrate a change in frequency, much less reasonable evidence of a causal association. Unsurprisingly, courts have rejected allegations seeking to avoid preemption based on the existence of adverse event reports in far greater numbers of reported adverse events than at issue here.

In *Gayle*, plaintiffs alleged that manufacturers needed to include specific warnings about the risk of diabetes, citing 6,000 adverse event reports (twenty-seven times as many adverse event reports than the 220 alleged here) as evidence of newly acquired information. 452 F. Supp. 3d at 87–89. "Plaintiffs offer[ed] no analysis on the adverse event reports. Instead, they merely proffer the adverse event reports by themselves to conclude that [defendant] could have updated the [] label." *Id.* at 88. Defendant moved for judgment on the pleadings. *Id.* at 83. The court granted defendant's motion holding that adverse event reports "do not reach any conclusions regarding a causal association," and therefore even *6,000* such reports "cannot constitute 'newly acquired information'" under a "plain reading" of the FDA's regulations. *Id.* at 88.[15] The court noted that other courts have even rejected the notion that "analyses based on adverse event reports—much less the reports standing along—can constitute 'newly acquired information.'" *Id.* at 88 (emphasis in original) (citing *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 663 (S.D.N.Y. 2017); *McGrath*, 393 F. Supp. 3d at 169); *see also MacMurray v. Boehringer Ingelheim Pharms., Inc.*, No. 2:17-CV-00195, 2017 WL 11496825, at *7–8 (D. Utah Dec. 6, 2017) (seventy-three adverse event reports insufficient to establish "newly acquired information" because nothing in the complaint suggested that they "would have been different from or greater in severity of frequency than" previously known adverse event reports). In sum, the court concluded that the mere number

[15] There is no "require[ment] that a causal relationship between a product and event" be established prior to reporting because "reports do not always contain enough detail to properly evaluate an event." FDA, Questions and Answers on FDA's Adverse Event Reporting System (FAERS) (June 4, 2018).

of adverse event reports, without putting them in context or without demonstrating they establish reasonable evidence of a causal association, do not satisfy the regulatory requirement.[16]

Plaintiffs have not alleged that these 220 adverse event reports show any change in "frequency" or "severity" of hearing-related adverse events—risks that were known to FDA and included in the 2020 Tepezza® Label—that would meet the regulatory requirement to demonstrate "newly acquired information," and the allegations in the complaint cannot support such an inference.

ii) Plaintiffs do not allege that the cited publications reveal risks of "greater severity or frequency."

Plaintiffs allege eighteen publicly-available publications—case reports, case series, observational studies, and a press release—that were available prior to the final exposure of the latest-infused of the nine Initial Bellwether Discovery plaintiffs. *See* FAC ¶¶ 99, 101, 105, 107–117. Plaintiffs do not, however, allege that this publicly available information indicated a greater frequency or severity of the condition at issue. Not a single paragraph in the complaints allege such an increase in frequency. Nor do the complaints allege an increase in severity. Plaintiffs also do not allege facts from which the Court could infer such changes.

[16] In any event, FDA has warned that spontaneous adverse event data of the kind plaintiffs allege "cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population." *See Questions and Answers on FDA's Adverse Event Reporting System (FAERS), U.S. Food & Drug Admin. (June 4, 2018)* https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers (**Exhibit H**). Courts have also concluded that adverse event reports do not establish a causal association. *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011); *see also Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1211 (10th Cir. 2002); *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989-990 (8th Cir. 2001).

The five case reports[17] or seven cases series[18] alleged by plaintiffs do not reveal "risks of . . . greater severity and frequency." 21 C.F.R § 601.12(f)(6). FDA was aware of reports from the clinical trials of hearing-related events that remained unresolved at the time FDA approved Tepezza®, including deafness.[19] Courts have routinely held that case reports and series discussing risks that FDA was already aware of—not risks of a different type or greater severity or frequency—do not constitute "newly acquired information."[20] *See McGrath,* 393 F. Supp. 3d at 169 ("[r]eports and studies that discuss" adverse events do not constitute "newly acquired information"); *see also Gibbons*, 919 F.3d at 708 (finding that plaintiffs' complaint "provides no basis" for the court to conclude that the bleeding events covered by alleged reports and studies were a different type of risk, or were more severe or more frequent than bleeding events the FDA already knew of); *Knight*, 984 F.3d at 338 (holding that plaintiff's claims were preempted because the study plaintiff alleged as new information did not reveal risks of a different type or greater severity or frequency of bleeding risk associated with Pradaxa than previously included in submissions to the FDA); *Lyons v. Boehringer Ingelheim Pharm., Inc.,* 491 F. Supp. 3d 1350, 1364 (N.D. Ga. 2020) (same); *Silverstein v. Boehringer Ingelheim Pharm., Inc.*, 9:19-cv-81188-RAR,

[17] *See* FAC ¶¶ 108 (case report of one patient), 112 (case report of one patient), 115 (case report of one patient), 116 (case report of one patient), 123 (case report of one patient).

[18] *Id.* ¶¶ 109 (case series of two patients), 111 (case series of four patients), 113 (prospective, observational case series of twenty-seven patients), 117 (review article of case reports), 122 (prospective cohort study of 35 patients), 127–129 (review of case reports); *see also, e.g.,* ¶¶ 67, 120, 263–265 (discussing the Expanded Access Protocol that provided access to teprotumumab to twenty-two patients who were ineligible for the clinical trials).

[19] *See* **Exhibit F** (Horizon's presentation to FDA) at 71 (noting patients with ongoing deafness and tinnitus); *see also* **Exhibit G** (FDA Advisory Committee transcript) at 264:14 to 265:8 (committee members discussing "patients that did not recover" and "a potential for irreversible change in one sense").

[20] Moreover, FDA had received five of the alleged publications, *see* FAC ¶¶ prior to September 30, 2022. *See* Articles Cited by the FDA's FAERS Database (**Exhibit I**). Accordingly, these publications, like the adverse event reports that were known to FDA, cannot constitute newly acquired information.

2020 WL 6110909, at *33–36 (S.D. Fla. Oct. 7, 2020) (same); *Pradaxa Cases*, No. CJC-16-004863, 2019 WL 6043513, at *3–4 (Cal. Super. Nov. 8, 2019) (same).

Even if plaintiffs allege that case series show an increase in the frequency of hearing-related adverse event reports, an allegation that there was a larger percentage of hearing-related adverse events in a small set of patients[21] does not allow the Court to make a reasonable inference that there was an overall increase in frequency in the entire post-marketing setting. Plaintiffs' only allegation regarding the frequency of hearing-related adverse events in the broader post-marketing setting is a single paragraph alleging that the Endocrine Society published a press release regarding the presentation of a "small study" that found "65% of patients on Tepezza suffer otologic symptoms include hearing loss and tinnitus." *See* FAC ¶¶ 99.b. The press release, however, does not support plaintiffs' allegation as it is nothing more than a limited case series discussing observations of a mere twenty-six patients.[22]

Nor can plaintiffs' allegations regarding seven observational review studies, much less the studies themselves, constitute newly acquired information satisfying the regulation.[23] Plaintiffs'

[21] *Id.* ¶¶ 111 (case series of four patients with hearing impairment out of twenty-eight treated patients), 113 (prospective, observational case series of twenty-seven patients, with five patients developing "teprotumumab-related hearing loss" and three patients with having continuing hearing impairment at last follow-up); *see also, e.g.,* ¶¶ 67, 120, 263–265 (discussing the Expanded Access Protocol that provided access to teprotumumab to twenty-two patients who were ineligible for the clinical trials).

[22] *See* Press Release, Endocrine Society, Increased risk of hearing impairment with new thyroid eye disease treatment (Mar. 20, 2021), https://www.endocrine.org/news-andadvocacy/news-room/featured-science-from-endo-2021/increasedrisk-of-hearing-impairment-with-new-thyroid-eye-disease-treatment **(Exhibit J)**; *see also* FAC ¶ 99b. (discussing Endocrine Society press release).

[23] FAC ¶ 99a. (describing TED treatment options and discussing the clinical trials), ¶ 99c. (analysis of clinical trials that confirmed hearing loss as one of most commonly reported adverse events at a rate of 10%), ¶ 101 (a follow-up, open-label extension clinical trial report of the OPTIC-X study for patients who were nonresponsive or who experienced a disease flare that confirmed hearing impairment at a rate of 10%), ¶ 105 (Winn, Teo, and Chern articles analyzing the clinical trials and confirming hearing loss as one of the most commonly reported adverse events at a rate of 10%), ¶ 105 (Girnita article discussing the roles of IGF-1 and TSH receptors in TED),107 (letter to the editor summarizing the clinical trials), ¶ 114 (first

allegations are based on reviews of the previously completed clinical trials, and commentary on TED and treatment options. Commentary on the underlying disease with no discussion, much less any allegation, regarding frequency or severity cannot constitute "newly acquired information." Plaintiffs do not even allege that these observational studies reveal "risks of … great severity and frequency." 21 C.F.R. § 601.12(f)(6). The FDA approved the 2020 Tepezza® Label after reviewing these same clinical trial data as indicated in FDA's approval letter. *See* Tepezza® BLA Approval Letter (**Exhibit K**);[24] *see also* **Exhibit C** at 1, § 6.1 "Clinical Trials Experience."

Finally, plaintiffs cite a February 22, 2022, Horizon press release that allegedly "demonstrated approximately 10% of all cases reported to the safety database have included a hearing-related event." *See* FAC ¶¶ 55–57. According to plaintiffs' allegations, the press release acknowledged what FDA already knew—that there is a 10% frequency of hearing impairment in patients treated with Tepezza®, which was observed in the pivotal clinical trials, and included in the original, 2020 Tepezza® Label in the "Clinical Trials Experience" section that FDA approved at launch. *Id.*; *see also* **Exhibit C** at § 6.1.

At bottom, there is simply no allegation that the cited information indicated a greater frequency or severity of the condition at issue. As a result, plaintiffs have failed to plausibly state a non-preempted claim. *In re Celexa & Lexapro*, 779 F.3d at 42; *Gibbons*, 919 F.3d at 708.

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practitioner consensus paper concerning guidelines for the use of Tepezza®), ¶ 124 (literature review of the clinical trials and observational studies reporting otologic adverse events with IGF-1/R inhibitors)

[24] *Tepezza® BLA Approval Letter*, U.S Food & Drug Admin. (Jan. 21, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/761143Orig1s000ltr.pdf (**Exhibit K**).

C. Plaintiffs' alleged information cannot establish "reasonable evidence of a causal association with a drug."

Submitted to FDA directly by the patient, doctor, or drug manufacturer, adverse event reports describe events that happened during or after a patient used a drug. *See* 21 C.F.R. § 600.80. Adverse event reports contain "[u]ncontrolled anecdotal information" and are considered "one of the least reliable sources" of support for a causation determination. *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005). Case reports (describing a single patient) and cases series (describing a small number of patients) that merely discuss adverse events without reaching any conclusion about a causal association with the medicine are not "newly acquired information." *McGrath,* 393 F. Supp. 3d at 169 (holding that "[r]eports and studies that . . . do not reach any conclusions regarding the adverse effects or risks" of a product cannot be "newly acquired information" that could support submitting a CBE warning change); *see also Rider*, 295 F.3d at 1199 (discussing the various problems with case reports and finding that case reports "cannot, standing alone, prove causation"). "Courts have also rejected the notion that analyses based on adverse event reports—much less the reports standing alone—can constitute 'newly acquired information.'" *Gayle*, 452 F. Supp. 3d at 88. Courts in the Seventh Circuit agree. *See, e.g.*, *R.S.B. ex rel. Hammar v. Merck & Co.*, No. 20-C-1402, 2022 WL 3927868, *3–4 (E.D. Wis. Aug. 31, 2022) (academic articles reporting on an adverse event associated with a drug did not constitute "newly acquired information" for purposes of 21 C.F.R. § 314.70). Accordingly, adverse event reports, case reports, and case series cannot, under 21 C.F.R. § 201.57(c)(6)(i), establish "reasonable evidence of a causal association with a drug."

In sum, plaintiffs' allegations do not allow "the court to draw the reasonable inference," *Iqbal*, 556 U.S. at 678, that Horizon was in possession of "newly acquired information" that revealed a greater frequency or severity of risk than previously included in Horizon's submissions

to FDA. Rule 8 "does not unlock the doors of discovery for a plaintiff armed with nothing more than conclusions" or conjecture. *Id.* at 678–79. Plaintiffs' claims are preempted.

CONCLUSION

For the foregoing reasons, the Court should grant this Motion and dismiss the First Amended Complaints of the nine Bellwether Discovery cases at issue in this Motion in their entirety.

Date: July 19, 2024

Respectfully Submitted,

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