UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen - ASD-ADHD Products Liability Litigation	:	22md3043 (DLC) 22mc3043 (DLC) 22cv8830 (DLC)
This Document Relates To: Chapman et al. v. Walmart, Inc. et al., 22cv8830	:	OPINION AND ORDER

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DENISE COTE, District Judge:

This Opinion addresses a motion to dismiss in this multidistrict products liability litigation ("MDL"). Cherise Chapman, individually and on behalf of her minor child D.C. (together, "Plaintiffs"), has sued Johnson & Johnson Consumer Inc. ("JJCI") and Walmart, Inc. ("Walmart"; collectively, "Defendants"), alleging that her child has autism spectrum disorder ("ASD") and attention-deficit/hyperactivity disorder ("ADHD") because Chapman used the Defendants' acetaminophen products while pregnant. The Plaintiffs allege that the Defendants violated the law of Nevada when they failed to warn of the risks of prenatal exposure to acetaminophen. For the following reasons, JJCI's motion to dismiss on the ground of preemption is denied.

Background

The following facts are drawn from the Plaintiffs' short form complaint ("SFC") and the master complaint in this MDL that the SFC incorporates by reference to the extent they are relevant to JJCI's motion to dismiss on the ground of preemption. The facts are taken as true for the purposes of this motion.

Chapman resides in Nevada. While pregnant, Chapman took Tylenol Extra Strength ("Tylenol"). Chapman's child was born in 2015 and has ASD and ADHD. Chapman asserts that, had she been

warned about the risk of ASD and ADHD, she would have taken less Tylenol or not taken it at all.

JJCI manufactures Tylenol. Acetaminophen has long been marketed as the only safe over-the-counter ("OTC") pain reliever for pregnant women. At the time Chapman took Tylenol, the label contained one warning related to pregnancy: "**If pregnant or breast-feeding**, ask a health professional before use." (Emphasis in original.) There was no specific warning about the risk of ASD or ADHD.

Several scientific studies have found prenatal exposure to acetaminophen to be associated with ASD and ADHD in children. The first cited study is from 2013. More studies followed.

On September 23, 2021, a group of 91 scientists, clinicians, and public health professionals published a "Consensus Statement." Ann Z. Bauer et al., Paracetamol Use During Pregnancy -- A Call for Precautionary Action, 17 Nature Revs. Endocrinology 757 (2021). In the Consensus Statement, the authors note:

> A growing body of experimental and epidemiological research suggests that prenatal exposure to paracetamol (N-acetyl-p-aminophenol (APAP), otherwise known as acetaminophen) might alter fetal development, which could in turn increase the risks of certain neurodevelopmental, reproductive and urogenital disorders. . . . [W]e believe we know enough to be concerned about the potential developmental risks associated with prenatal APAP exposure and therefore call for precautionary action.

Id. at 758-59. Among the "adverse neurodevelopmental outcomes" the Consensus Statement identifies are ASD and ADHD. Id. at 762. The signatories conclude:

> [W]e believe the combined weight of animal and human scientific evidence is strong enough for pregnant women to be cautioned by health professionals against its indiscriminate use, both as a single ingredient and in combination with other medications. We recommend that APAP should be used by pregnant women cautiously at the lowest effective dose for the shortest possible time. Long-term or high-dose use should be limited to indications as advised by a health professional. Packaging should include warning labels including these recommendations.

Id. at 764.

On June 7, 2022, the Plaintiffs filed this action in the U.S. District Court for the District of Nevada. On October 5, the Judicial Panel on Multidistrict Litigation consolidated this action with others asserting claims that prenatal exposure to acetaminophen causes ASD and ADHD in children and transferred the cases to this Court under 28 U.S.C. § 1407. On November 14, motions to dismiss two actions within the MDL on the ground of preemption were denied. In re Acetaminophen - ASD-ADHD Products Liability Litigation, No. 22md3043 (DLC), 2022 WL 17348351 (S.D.N.Y. Nov. 14, 2022) ("November Opinion").

At the November 17 initial pretrial conference, a schedule was set for the filing of two master complaints: one naming JJCI and the other naming Retailer Defendants. On December 16, the MDL plaintiffs filed the master complaint against JJCI.

On January 20, 2023, Chapman filed her SFC, and on February 3, timely amended it. The SFC asserts Nevada state law claims against JJCI, to wit, claims for strict liability for failure to warn, strict liability for design defect due to inadequate warnings and precautions, negligence, negligent misrepresentation, breach of implied warranty, and violation of Nevada's consumer protection laws.[1]

On February 10, JJCI moved to dismiss all of the SFCs filed against it, including Chapman's.[2] The motion became fully submitted on March 17.

The Retailer Defendants also moved to dismiss all the SFCs filed against them. Separate Opinions will address those motions.

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[1] The Plaintiffs also assert a strict liability misrepresentation claim under the laws of states in which the Plaintiffs do not reside, including California. The SFC does assert, however, in its claim against Walmart, that Chapman purchased Walmart's store-branded acetaminophen in Sacramento, California.

[2] The Court has advised counsel that motions to dismiss should be brought against particular complaints and not against the master complaint. The master complaint is not the operative pleading; it is an administrative document. See Bell v. Publix Super Markets, Inc., 982 F.3d 468, 490 (7th Cir. 2020). JJCI's motion has been styled as brought against all complaints filed in the MDL. The Court, therefore, has chosen the Chapman SFC for this Opinion because it asserts claims against both JJCI and a Retailer Defendant, alleges that the acetaminophen taken by Chapman caused her child to develop both ASD and ADHD, and alleges that the acetaminophen products were taken before 2017.

Discussion

JJCI asserts that federal law preempts the Plaintiffs' state law claims. A multidistrict litigation transferee court "applies the substantive state law, including choice-of-law rules, of the jurisdiction in which the action was filed." Desiano v. Warner-Lambert & Co., 467 F.3d 85, 91 (2d Cir. 2006) (citation omitted). This action was filed in Nevada.

Nevada has adopted the "most significant relationship test" from the Restatement (Second) of Conflict of Laws for choice-of-law decisions in tort actions. General Motors Corp. v. Eighth Judicial Dist. Ct. of State of Nev. ex rel. County of Clark, 134 P.3d 111, 116 (Nev. 2006). Based on the facts asserted in the SFC, it appears that Nevada has the most significant relationship to this litigation. It alleges that the Plaintiffs reside in Nevada. Nevada's tort laws will be applied here. To be clear, no party has argued that the choice of law inquiry will affect the preemption analysis, and nothing that follows suggests that it should.

Under Nevada law, a failure to warn claim consists of the following elements: "(1) the product had a defect which rendered it unreasonably dangerous, (2) the defect existed at the time the product left the manufacturer, and (3) the defect caused the plaintiffs injury." Motor Coach Indus., Inc. v. Khiabani by and through Rigaud, 493 P.3d 1007, 1011 (Nev. 2021) (citation

omitted). "[T]he lack of a warning functions as the relevant [product] defect." Id.

At the heart of the Plaintiffs' complaint is the assertion that JJCI had a duty under state law to warn of the risks of prenatal exposure to acetaminophen. JJCI asserts that this state law duty is preempted by regulations promulgated by the Food and Drug Administration ("FDA") that govern how OTC drugs are manufactured and marketed to consumers and by the prohibition in the Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399g ("FDCA"), on misbranding. Before discussing the jurisprudence on preemption, it is helpful to review the FDA regulatory scheme for new drugs and OTC drugs generally and the federal regulation of acetaminophen.[3]

I. FDA Regulatory Scheme for New Drugs and OTC Drugs

"The federal government regulates the manufacture, labeling, and sale of pharmaceuticals pursuant to the" FDCA. Gibbons v. Bristol-Meyers Squibb Co., 919 F.3d 699, 707 (2d Cir. 2019). No drug can enter interstate commerce "unless [the] FDA determines that it is generally recognized as safe and effective ("GRAS/E") for the particular use described in its product labeling." Nat. Res. Def. Council, Inc. v. U.S. FDA, 710 F.3d

[3] This discussion largely repeats that contained in the Court's first Opinion addressing a preemption argument in this MDL. See November Opinion, 2022 WL 17348351, at *3-*6.

71, 75 (2d Cir. 2013) (addressing new drug regulation). Once a drug is deemed GRAS/E, it is a "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." Wyeth v. Levine, 555 U.S. 555, 570-71 (2009).

The FDCA prohibits "the introduction into interstate commerce of any" misbranded drug. 21 U.S.C. § 331(a). Under the FDCA, a drug is misbranded "if its labeling is false or misleading in any particular" or does not bear "adequate warnings . . . against use . . . where its use may be dangerous to health." Id. § 352(a)(1); (f)(2). The misbranding prohibition is enforced through administrative, civil, and criminal actions. See id. §§ 332-33; 371-72. The FDA has "complete discretion" to decide when the FDCA's enforcement provisions should be exercised. Heckler v. Chaney, 470 U.S. 821, 835 (1985).

"In the 1930's, Congress became increasingly concerned about unsafe drugs and fraudulent marketing," and it enacted the FDCA. Wyeth, 555 U.S. at 566. "The FDCA's most substantial innovation was its provision for premarket approval of new drugs." Id. A new drug is defined as:

> any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed,

> recommended, or suggested in the labeling thereof . . . .

21 U.S.C. § 321(p)(1). "[A] manufacturer seeking federal approval to market a new drug must prove that it is safe and effective and that the proposed label is accurate and adequate." PLIVA, Inc. v. Mensing, 564 U.S. 604, 612 (2011). Manufacturers may obtain federal approval by submitting a new drug application ("NDA"). Wyeth, 555 U.S. at 566. "The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label." Id. at 568. Drugs approved through the NDA process are commonly referred to as brand-name drugs.

After an NDA is approved, the FDA permits a brand-name drug manufacturer to "make certain changes to its label before receiving the agency's approval" through the changes being effected ("CBE") regulation. Id. The CBE regulation allows a manufacturer to change a drug label to "reflect newly acquired information." 21 C.F.R. § 314.70(c)(6)(iii). These changes include those that "add or strengthen a contraindication, warning, precaution, or adverse reaction [or that] add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." Wyeth, 555 U.S. at 568 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A), (C)). Overall, then, a brand-name drug manufacturer "is charged

both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[4] Id. at 571.

In 1972, the FDA developed a separate regulatory process, known as the monograph system, for the approval of classes of OTC drug products and their active ingredients. As the Second Circuit has explained:

> Commenced in 1972, the OTC Drug Review established FDA's "monograph" system for regulating over-the-counter drugs. While FDA must generally approve drugs as GRAS/E individually, the monograph system allows manufacturers to bypass individualized review. Under this system, FDA issues a detailed regulation -- a "monograph" -- for each therapeutic class of OTC drug products. Like a recipe, each monograph sets out the FDA-approved active ingredients for a given therapeutic class of OTC drugs and provides the conditions under which each active ingredient is GRAS/E.

NRDC, 710 F.3d at 75 (citation omitted).

The monograph system establishes conditions under which certain classes of drugs will be considered GRAS/E and not misbranded.[5] Critically, if the drug meets the required

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[4] In 1984, the FDA created a process by which generic drugs can gain FDA approval "simply by showing equivalence to a reference listed drug that has already been approved by the FDA." Mensing, 564 U.S. at 612; see also FTC v. Shkreli, 581 F. Supp. 3d 579, 594 (S.D.N.Y. 2022). Generic drugs labels must "be the same at all times as the corresponding brand-name drug labels." Mensing, 564 U.S. at 618. Therefore, unlike brand-name drugs, the labels for generic drugs cannot be unilaterally changed. Id. at 614.

[5] The regulations provide that

conditions and is therefore GRAS/E, it is not a "new drug" that requires premarket approval. Conversely, any drug covered by the monograph system that does not conform to the conditions "is liable to regulatory action." 21 C.F.R. § 330.1; see also Over-the-Counter Drug Monograph System -- Past, Present, and Future; Public Hearing, 79 Fed. Reg. 10168, 10169 (Feb. 24, 2014).

From 1972 to 2020, the monograph system involved four regulatory steps: (1) an advisory review panel was established to evaluate the safety and effectiveness of the OTC drug; (2) the advisory review panel submitted its report to the FDA Commissioner; (3) the FDA published a tentative final monograph ("TFM"); and (4) after receiving comments on the TFM, the FDA published a final monograph. 21 C.F.R. § 330.10. The monographs, then, set out the conditions with which manufacturers had to comply in order to bypass the NDA process.

The monograph system was reformed as a part of the Coronavirus Aid, Relief, and Economic Security Act, Pub. L. 116-136, 134 Stat. 281 (2020) ("CARES Act"). See Final Administrative Orders for Over-the-Counter Monographs;

> [a]n over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph.

21 C.F.R. § 330.1.

Availability, 86 Fed. Reg. 52474, 52474-75 (Sept. 21, 2021). The rulemaking process governing monographs "was replaced with an administrative order process." Id. at 52475. The CARES Act also made existing TFMs final orders if they met certain conditions. See 21 U.S.C. § 355h. Lastly, the CARES Act created a process by which drug manufacturers can request that the FDA issue administrative orders stating that a drug is GRAS/E or that a change to a condition of use of a drug is GRAS/E. Id. § 355h(b)(5)(B).

II. FDA Regulation of Acetaminophen

Acetaminophen is regulated under the monograph system. Therefore, drug labels for acetaminophen must comply with the relevant monograph and OTC drug labeling requirements. 21 C.F.R. § 330.1. This section of the Opinion will discuss the monograph and the OTC drug labeling requirements separately, with a focus on the regulations that speak to pregnancy.

A. Monograph Governing Acetaminophen

In 1988, the FDA published a TFM that regulated internal analgesic, antipyretic, and antirheumatic ("IAAA") drug products. See Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph, 53 Fed. Reg. 46204 (Nov. 16, 1988) ("IAAA TFM"). As a TFM, the document's legal status was that of

a proposed rule. Id. at 46204. It invited written comments, objections, or requests for a hearing. Id.

The IAAA TFM defines analgesics as drugs "used to alleviate pain and reduce fever." Id. at 46255. Among the analgesics described in the IAAA TFM were acetaminophen and aspirin. Id. Since 1988, the FDA has proposed amendments to the IAAA TFM and finalized certain sections,[6] but until the passage of the CARES Act, many of the sections relating to acetaminophen remained tentative.

The IAAA TFM states that a drug product containing acetaminophen as the active ingredient is "generally recognized as safe and effective and is not misbranded if it meets each of the conditions in" the TFM and 21 C.F.R. § 330.1. Id. at 46255. One of the conditions is that "the labeling of the product contains the following statements under the heading 'Warnings.'" Id. at 46256. For IAAA drug products that contain acetaminophen as the active ingredient, the IAAA TFM does not include a warning specific to pregnancy. The IAAA TFM does, however, include pregnancy warnings for analgesics containing other active ingredients, such as aspirin. Id.

[6] For example, the FDA finalized a monograph relating to the professional labeling of IAAA products containing aspirin in 1998. See 21 C.F.R. pt. 343.

The IAAA TFM became a final order effective March 27, 2020 under the CARES Act. The FDA published the IAAA TFM, as amended in the years since 1988, as a final administrative order on October 14, 2022. U.S. Food and Drug Administration, Over-the-Counter (OTC) Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (Oct. 14, 2022).

B. OTC Drug Labeling Requirements

Drugs regulated under the monograph system are required to comply with the FDA's regulations for drug labeling, including those regulating OTC drug labels. 21 C.F.R. § 330.1(c)(1) (incorporating 21 C.F.R. § 201.66). Where warnings required by regulation are "established and identified by quotation marks," the language on the drug label must be in the "exact language" established by regulation. Id. § 330.1(c)(2) ("Exact Language Regulation"); see also Labeling of Drug Products for Over-the-Counter Human Use, 51 Fed. Reg. 16258, 16263 (May 1, 1986).

When the FDA finalized § 201.66 in 1999, it explained that several manufacturers had asked the FDA to "allow voluntary warnings to appear under the appropriate headings to further protect consumers from possible misuse of the product." Over-the-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. 13254, 13271 (Mar. 17, 1999). In response, the FDA encouraged

> manufacturers to discuss with the agency the addition of voluntary warnings to OTC drug products. As a general matter, FDA agrees that consumers may be confused if an appropriate warning were placed outside of the Drug Facts area.[7] Thus, the agency expects such warnings to appear under the "Warnings" heading, preceded by an appropriate subheading.

Id. (emphasis supplied).

C. Pregnancy Warning for Acetaminophen

The regulations for OTC drug labels include the requirement that all OTC drug products intended for systemic absorption contain a pregnancy and breast-feeding warning.[8] 21 C.F.R. § 201.63. A brief history of the Pregnancy Warning provides context for the regulation.

In 1982, the FDA finalized a regulation adding a "pregnancy-nursing warning" for OTC drugs that were "intended for systemic absorption." Pregnant or Nursing Women; Delegations of Authority and Organization; Amendment of Labeling Requirements for Over-the-Counter Human Drugs, 47 Fed. Reg. 54750, 54757 (Dec. 3, 1982). The warning read: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." Id. at 54758.

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[7] The Drug Facts area refers to the section of a drug's label in which regulated content appears. See 21 C.F.R. § 201.66(b)(10); (c)(1).

[8] 21 C.F.R. § 201.63 will be referred to as the Pregnancy Warning Regulation. The text of the warning that manufacturers must include on certain OTC drug labels will be referred to as the Pregnancy Warning.

This regulation was incorporated into the regulations for drugs manufactured and sold under the monograph system. Id.; 21 C.F.R. § 330.2.

In 1999, the Pregnancy Warning was amended and assumed its current form as a part of a final rule that added many additional requirements for OTC drug labels.[9] Over-the-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. at 13286. The Pregnancy Warning Regulation states:

> The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) as follows: "If pregnant or breast-feeding, ask a health professional before use." [first four words of this statement in bold type] In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.

21 C.F.R. § 201.63(a). The Pregnancy Warning is mandatory unless an NDA or final monograph states otherwise, id. § 201.63(b), or the FDA grants a manufacturer an exemption. Id. § 201.63(d).

III. Preemption Standard

With the framework for the federal regulation of OTC acetaminophen described, the law of preemption can be summarized. "The Supremacy Clause establishes that federal law

[9] The express incorporation of the Pregnancy Warning for OTC drug labels is governed by § 210.66(c)(5)(ix).

'shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.'" Mensing, 564 U.S. at 617 (quoting U.S. Const., art. VI, cl. 2). One type of preemption is conflict preemption, and it is on that doctrine that JJCI relies. See Grand River Enters. Six Nations, Ltd. v. Boughton, 988 F.3d 114, 125-26 (2d Cir. 2021) (explaining the three types of preemption).

"Where federal and state law conflict -- that is, where it is impossible for a party to follow both federal and state law -- state law must give way." Gibbons, 919 F.3d. at 708. As the Supreme Court has observed, "[i]mpossibility pre-emption is a demanding defense." Wyeth, 555 U.S at 573. JJCI "must show that federal and state laws directly conflict." Grand River, 988 F.3d at 126 (citation omitted).

Neither the Supreme Court nor any circuit court has addressed preemption in the context of the Pregnancy Warning or the monograph system. Three Supreme Court decisions involving preemption and FDA regulation of prescription drugs through the NDA process nevertheless provide helpful guidance. In Wyeth, the Court found that the FDCA does not preempt state law failure to warn claims against manufacturers of brand-name drugs marketed pursuant to NDAs. 555 U.S. at 581. The Court reasoned that because a brand-name manufacturer can "unilaterally

strengthen" warnings on its label through the CBE process, it is not impossible for a manufacturer to comply with both state and federal law. Id. at 573. The Court also rejected the argument that changing the label would have rendered the drug misbranded and thus in violation of federal law. Id. at 570. The Court noted, however, that "clear evidence that the FDA would not have approved a change to" an NDA-approved drug label may warrant a finding of preemption. Id. at 571.

Next, in Mensing, the Court held that the FDCA does preempt state law failure to warn claims brought against generic drug manufacturers. 564 U.S. at 609. The Court emphasized that generic drug manufacturers are required by FDA regulations to have the same label as the brand-name drug, so they cannot unilaterally change their labels without violating FDA regulations. See id. at 612-13. Lastly, in Mutual Pharmaceutical Co., Inc. v. Bartlett, the Court expanded Mensing and held that the FDCA also preempts state law design-defect claims brought against generic drug manufacturers. See 570 U.S. 472, 476 (2013). Thus, if a defendant could have unilaterally strengthened warnings on its label without prior approval from the FDA, a state law failure to warn claim is not preempted. Gibbons, 919 F.3d at 708.

Recently, in Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019), the Court elaborated on the "clear evidence"

standard identified in Wyeth. The Court held that the question of whether there is "clear evidence" that the FDA would not have approved a change to a drug's label is a question for the judge, not a jury, to decide. Id. at 1672. Albrecht described "clear evidence" as evidence "that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law" and the FDA nonetheless "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." Id.

Albrecht addressed these issues, like the trilogy of Supreme Court decisions just discussed, in the context of a prescription drug and the FDA regulations that apply to drugs that receive approval through an NDA or the generic versions of those drugs. In that context, it discussed the CBE regulations that permit changes to a drug label and observed that a drug manufacturer "will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." Id. at 1679. To succeed with a preemption defense, the manufacturer must present clear evidence in the form of "agency actions taken pursuant to the FDA's congressionally delegated authority." Id. As examples of such delegated authority, the Court referred to the FDA's rulemaking authority over labeling, and its authority to formally reject a new warning through the CBE process. Id.

IV. Application

JJCI has moved to dismiss this action, and indeed all of the actions filed against it in this MDL, on the ground that the state law claims are preempted. For the reasons explained below, and in the November Opinion, the Plaintiffs' claims are not preempted. The dispositive question is: could JJCI have added a truthful warning about the risks of in utero exposure to acetaminophen labels without violating federal law? The answer is yes.

Before describing JJCI's arguments, it is important to emphasize what JJCI is not arguing. JJCI does not contend that it is without responsibility for the contents of its drug labels. It agrees that it has the authority to voluntarily add appropriate, truthful warnings to its labels, whether those are for acetaminophen or any other OTC drug. Therefore, it is not asserting that state law product liability claims are generally preempted. Its argument is much narrower. It contends that it may not further warn consumers about the risks of taking acetaminophen during pregnancy because the FDA has already spoken about that specific risk and required consumers to be warned that they should consult a healthcare professional before using acetaminophen. JJCI argues that only that narrower class of claims is preempted. Against this background, JJCI's three arguments in support of its preemption argument are as follows.

First, JJCI argues that FDA regulations require JJCI to use the Pregnancy Warning without any alteration on its label and thereby prohibit JJCI from adding any other pregnancy-related warning. Second, it argues that the additions to the label the Plaintiffs seek here would have rendered its acetaminophen misbranded under federal law. Finally, it argues that, since the FDA would have rejected any effort by JJCI to use the CBE regulation to change the label for any of its acetaminophen products approved under an NDA, it "would make no sense" for a different warning to appear on monograph-approved acetaminophen. Each theory of preemption will be discussed in turn.

A. The Pregnancy Warning

JJCI rests its first preemption argument on the command in the Exact Language Regulation that any warning in OTC drug labeling must use "the exact language" that the FDA has prescribed "where such exact language has been established and identified by quotations marks in an applicable OTC drug monograph or by regulation." 21 C.F.R. § 330.1(c)(2). It is undisputed that the Pregnancy Warning is identified by quotation marks and the Exact Language Regulation therefore requires JJCI to include the Pregnancy Warning precisely as dictated by the FDA in its regulation of all OTC medication that is "intended for systemic absorption." Id. § 201.63(a). Thus, OTC acetaminophen products must include the warning: "**If pregnant**

or breast-feeding, ask a health professional before use." (Emphasis in original.)

The requirement that JJCI include and not alter the Pregnancy Warning does not, however, preempt the Plaintiffs' claims. It is a foundational principle for OTC drugs, as it is for brand-name drugs issued through an NDA process, that a manufacturer is responsible for the adequacy of the warnings on its drug label. See Wyeth, 555 U.S. at 570-71. And, because the FDA regulatory scheme permits drug manufacturers to change their labels, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." Albrecht, 139 S. Ct. at 1679. Neither the Exact Language Regulation nor the Pregnancy Warning Regulation alter the responsibility or opportunity to ensure that the acetaminophen label is adequate.

The Pregnancy Warning Regulation does not contain language purporting to limit a manufacturer's obligation to ensure that its label is adequate, including in the warnings on its label. See 21 C.F.R. § 201.63. The Pregnancy Warning itself contains no language indicating that the Pregnancy Warning is exclusive. A manufacturer of acetaminophen can satisfy its obligation to include the Pregnancy Warning precisely as written in the regulation while also complying with a state law duty to warn.

If JJCI were correct that it is not free to add truthful warnings related to the use of acetaminophen during pregnancy, then that would mean that all manufacturers of OTC monograph-approved drugs intended for systemic absorption would be similarly barred from adding to their labels truthful warnings about use of their own drugs during pregnancy. This would constitute a massive shift from a foundational principle underlying federal drug regulation that manufacturers are responsible at all times for the adequacy of their drug labels. See Wyeth, 555 U.S. at 570-71. Nothing in the Pregnancy Warning Regulation purports to enact such a sweeping change to FDA policy.

In support of its argument about the exclusivity of the Pregnancy Warning, JJCI makes several arguments. First, relying on the Pregnancy Warning Regulation, JJCI contends that the FDA's ability to replace the general Pregnancy Warning with warnings regarding use of specific drugs during pregnancy, and its failure to add such a specific warning for acetaminophen through the IAAA TFM or otherwise, should be understood as a determination by the FDA against adding the warning the Plaintiffs argue that state law requires. The FDA's silence regarding an acetaminophen-specific warning does not preempt state law.

The FDA's authority to include a specific warning is recognized in the Pregnancy Warning Regulation, a regulation that applies to all drug products intended for systemic absorption. See 21 C.F.R. § 201.63(b). For ease of reference, the relevant provisions of the Pregnancy Warning Regulation are repeated here:

> (a) The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) as follows: "If pregnant or breast-feeding, ask a health professional before use." [first four words of this statement in bold type] In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.
>
> (b) Where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph in part 330 of this chapter, the specific warning shall be used in place of the warning in paragraph (a) of this section, unless otherwise stated in the NDA or in the final OTC drug monograph.

Id. § 201.63(a)-(b) (emphasis supplied).

Subsection (a) requires that users be cautioned to consult a health professional before using systemically absorbed OTC drug products during pregnancy. Subsection (b) of the Pregnancy Warning Regulation requires a manufacturer to include on a label a specific warning related to pregnancy "in place of" the general warning required by § 201.63(a) when the specific warning is required by the drug's NDA or monograph. Id. §

201.63(b). The Pregnancy Warning Regulation simply does not speak to whether a further warning related to a drug's use during pregnancy can be added to the general Pregnancy Warning on a drug label, whether added by the FDA or added by a manufacturer. This regulation does not, therefore, preempt state law to the extent state law may require additional warnings about the use of acetaminophen during pregnancy, for instance by referring to specific risks associated with taking acetaminophen.

JJCI next argues that, because the Pregnancy Warning Regulation explains when a symbol may be used alongside the Pregnancy Warning, the FDA meant to prohibit any other additional warnings not expressly permitted by the regulation. Id. § 201.63(a). As JJCI puts it, if a manufacturer were free to add any additional warning, whether a symbol or text, it would have been unnecessary for the FDA to give such explicit permission to use a symbol. As explained in the November Opinion, during the 1982 rulemaking process that resulted in the Pregnancy Warning Regulation, the FDA responded to concerns that the Pregnancy Warning may not reach those who are not literate in English. See November Opinion, 2022 WL 17348351, at *9. The adoption of a proposal during the rulemaking process that a symbol be permitted to improve the reach and impact of the Pregnancy Warning, a warning that is required for all

systemically absorbed OTC drug products, cannot be construed as a ban by this regulation on any other improvements to warnings, including on any of the labels for any specific systemically absorbed OTC drug. The FDA's approval of the use of a symbol to emphasize the Pregnancy Warning does not mean that Nevada's products liability laws directly conflict with the Pregnancy Warning Regulation if those laws require warnings to be added to the acetaminophen label.

JJCI next argues that a finding of preemption would be consistent with the FDA's discussion during its formulation of the Pregnancy Warning of the importance of uniformity in the warnings given to American consumers. It points to the FDA's emphasis during the rulemaking process on there being a "single national warning" for use of systemically absorbed OTC drugs during pregnancy, and its determination that more specific warnings for particular drugs or classes of drugs be "handled" in OTC monographs. That regulatory history is described in the November Opinion. See November Opinion, 2022 WL 17348351, at *9. While there may be many strong policy reasons in favor of uniform warnings, see id. at *10, the legal issue is whether the Nevada state law claims are preempted by the Pregnancy Warning Regulation. For the reasons already explained, they are not.

JJCI next relies on certain statements made by the FDA during the rulemaking process that resulted in the Exact

Language Regulation. JJCI contends that the FDA's reference to "exclusivity" indicates that the agency viewed the FDA-approval procedures as the only mechanism through which warnings could be altered or through which warnings could be added. This argument misconstrues both the text of the Exact Language Regulation and the history behind its creation.

In general, OTC drug labels have several sections with text that is subject to regulation, such as "Uses," "Warnings," "Directions," "Other Information," and "Inactive Ingredients." Regulation 330.1(c)(2) provides that where the FDA has identified a warning by quotation marks and required it to be included on a label, that warning must be replicated exactly as indicated by those quotation marks. It cites as an example the Pregnancy Warning. And, where the FDA has identified appropriate indications for the drug, those indications need not be repeated verbatim. The indications can be written as the entity wishes in the Uses section of the label so long as those indications are included in a way that is not misleading. The regulation provides:

> The "Uses" section of the label and labeling of the product shall contain the labeling describing the "Indications" that have been established in an applicable OTC drug monograph or alternative truthful and nonmisleading statements describing only those indications for use that have been established in an applicable monograph, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the

> introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act. Any other labeling under this subchapter and subchapter C et seq. of this chapter shall be stated in the exact language where exact language has been established and identified by quotation marks in an applicable OTC drug monograph or by regulation (e.g., § 201.63 of this chapter), except as provided in paragraphs (i) and (j) of this section.

21 C.F.R. § 330.1(c)(2)(emphasis supplied).

Before this regulation was issued, it was the FDA's policy to limit labels for drugs approved through monographs to "specific words and phrases considered and approved by FDA." Labeling of Drug Products for Over-the-Counter Human Use, 50 Fed. Reg. 15810, 15810 (Apr. 22, 1985). Following objections and a public hearing, the FDA concluded that the "exclusivity policy, while legally supportable, should not be continued for policy reasons." Id. at 15811.

The FDA finalized this decision in a 1986 rule, a predecessor to the Exact Language Regulation, which was issued in its current form in 1999. In its accompanying statement to the 1986 rule, the FDA explained its change in position:

> Recognizing that, within limits, there can be various ways of accurately stating the same thing, some of which may even be more meaningful to potential purchasers of OTC drug products, the agency has concluded that it can meet its responsibilities by providing greater flexibility for the use of alternative truthful statements without recourse to the time- and resource-consuming monograph amendment process.

Labeling of Drug Products for Over-the-Counter Human Use, 51 Fed. Reg. at 16259.

Thus, the Exact Language Regulation explains when manufacturers must use the labeling content, as described in a drug's monograph, verbatim and when non-misleading variations are permitted. The regulation does not address, much less bar, additions to the warnings on a label. In the context of the Pregnancy Warning, for example, the drug label must say "health professional"; it may not say "doctor." Should state law require additions to a label's warnings that do not conflict with the Pregnancy Warning's direction to consult with a health professional before using acetaminophen, the Exact Language Regulation would not preempt those additions.

Finally, JJCI argues that there is a strong federal policy against "overwarning." See Albrecht, 139 S. Ct. at 1673 (noting that the hierarchy of label information is "designed to 'prevent overwarning'"). That is no doubt so, and for good reason, but again, that does not require a finding that any and all additions to the Pregnancy Warning that may be supported by science and required by state law are preempted. See November Opinion, 2022 WL 17348351, at *10. Indeed, in 1999, as explained above, the FDA encouraged manufacturers to discuss with the FDA the addition of voluntary warnings to OTC drug

labels. See Over-the-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. at 13271.

B. Prohibition on Misbranding

JJCI argues that there is a second reason that the Plaintiffs' claims are preempted. The products at issue here are subject to the law against misbranding. 21 U.S.C. § 331(a). From this it concludes that any additions to the Pregnancy Warning sought by the Plaintiffs would render the label false or misleading, and subject JJCI to a legal enforcement action by the FDA. This second preemption argument also fails.

The Supreme Court addressed this very argument in Wyeth.[10] As the Supreme Court observed, "[t]he FDCA does not provide that a drug is misbranded simply because the manufacturer has altered an FDA-approved label; instead, the misbranding provision focuses on the substance of the label and, among other things, proscribes labels that fail to include 'adequate warnings.'" Wyeth, 555 U.S. at 570 (citing 21 U.S.C. § 352(f)). "[T]he very idea that the FDA would bring an enforcement action against a

[10] JJCI argues that the reasoning in Wyeth does not apply to monograph-approved drugs because a manufacturer "has far less leeway to alter the label of a drug approved under a monograph" than one approved through the NDA process. JJCI does not explain why that is so. As discussed throughout this Opinion, there is no federal regulatory bar to strengthening a label's warnings for monograph-approved drugs.

manufacturer for strengthening a warning . . . is difficult to accept." Id.

Here, it is premature to conclude that the addition of the warning the Plaintiffs may seek to add to an acetaminophen label would render the label misbranded. To begin with, the parties hotly dispute what conclusions can be fairly drawn from currently available scientific research. Daubert motion practice will take place this Fall. From that motion practice it may become clearer whether any additional warning may and/or should be added to the acetaminophen label.

JJCI contends it is not premature to find that the additional warning the Plaintiffs may seek here will be rejected by the FDA. JJCI points out that the FDA rejected California's proposed label change connecting acetaminophen to cancer, and found that its inclusion would misbrand the products and was preempted.[11] While the FDA clearly rejected the California proposal, its views on the issues presented by this MDL are not so clearly stated.

[11] Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch. to Julian Leichty, Off. of the Env't Health Hazard Assessment (Nov. 4, 2019), https://oehha.ca.gov/media/dockets/19653/19710-u.s._food_and_drug_administration_fda/fda_comments_notice_of_availability_of_hazard_identification_materials_for_acetaminophen_1142019.pdf.

JJCI points to several statements by the FDA, or components of the FDA, expressing reservations about the studies that have been done of the risks of prenatal exposure to acetaminophen, and about the need to add warnings to the labels concerning those risks. In a 2015 Drug Safety Communication ("2015 DSC"),[12] the FDA stated:

> We found all of the studies we reviewed to have potential limitations in their designs; sometimes the accumulated studies on a topic contained conflicting results that prevented us from drawing reliable conclusions. As a result, our recommendations on how pain medicines are used during pregnancy will remain the same at this time.[13]

Through a FOIA request, JJCI has obtained a 2017 internal Memorandum of Consultation by the FDA's Division of Bone, Reproductive, and Urologic Products ("DBRUP") to its Division of Nonprescription Drug Products regarding "Public communication about in utero acetaminophen exposure and the potential for adverse neurodevelopmental outcomes." The memorandum concludes:

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[12] A Drug Safety Communication or DSC is an FDA communication with the public "intended to provide important information to patients and health care professionals about new safety issues with the medicines they are taking or prescribing so they can make more informed decisions about treatment." Drug Safety Communications, U.S. Food & Drug Admin., https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications (Apr. 13, 2023).

[13] U.S. Food & Drug Administration, FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy 1-2 (Jan. 9, 2015), https://www.fda.gov/media/90209/download.

> In sum, we acknowledge the consistency of the findings of positive association between APAP and adverse neurodevelopmental outcomes in the majority of the published observational studies reviewed to date. Although we have more studies, we do not have higher quality data to better inform drug causality and what these findings mean in clinical practice. All of these studies had significant limitations, uncertainties, and critical missing information that preclude reliable inference of drug attribution. Thus, we are unable to draw any conclusion about the causal association between prenatal APAP exposure and the different adverse neurodevelopmental outcomes, based on the available evidence.
>
> DBRUP does not believe the available observational evidence merits updating the 2015 DSC . . . with more definitive conclusions, such as a "possibility" of causation, about drug causality of APAP and adverse neurodevelopmental outcomes. . . . [W]e believe it is reasonable to consider updating the 2015 DSC to indicate that FDA has evaluated additional publications on APAP and neurobehavioral/developmental outcomes in the offspring. The updated DSC, however, should retain the same FDA conclusion about the inability to draw reliable conclusions about drug causality and clinical recommendations stated in the 2015 DSC.[14]

Since 2017, more scientific research has been published, including the Consensus Statement highlighted in the master complaint. The FOIA disclosures from the FDA indicate that the agency continues to evaluate that research.

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[14] Memorandum from Christine P. Nguyen, Deputy Dir. for Safety, & Audrey Gassman, Deputy Dir., Div. of Bone, Reprod., & Urologic Prods. to Janice Adams-King, Regul. Projects Manager, Div. of Nonprescription Drug Prods. 11-12 (Feb. 10, 2017).

In 2022, for example, the FDA's Office of Pharmacovigilance and Epidemiology created a Review of Published Studies addressed to "Functional Neurobehavioral Outcomes and Urogenital Outcomes Associated with Prenatal Acetaminophen Exposure." The review concludes:

> Overall, there are still study limitations and inconsistent study findings that prohibit causal interpretations of the association between APAP exposure and functional neurobehavioral outcomes as well as urogenital outcomes. Studies, including meta-analyses, consistently note associations between APAP and ADHD; however, associations are inconsistent by trimester of exposure. The most methodologically rigorous study found a weak association between overall APAP and long durations of APAP use and behavioral problems. The prior FDA communication focused on medication use for pain during pregnancy and did not discuss amount of use. As a result, it may be prudent, as a precautionary measure, to issue a communication emphasizing that APAP use in pregnancy should be judicious. The communication may also want to discuss APAP use for fever during pregnancy. Untreated fevers during pregnancy are associated with poor pregnancy outcomes; there is some evidence that treatment of fever during pregnancy may attenuate these risks or be protective.[15]

(Emphasis supplied.)

On April 19, 2023, the Court extended an invitation to the United States, and to the FDA, to respond to the following two questions:

1. Should the Plaintiffs' Proposed Warning be added to

[15] Danielle Abraham & Andrew D. Mosholder, Food & Drug Admin., Epidemiology: Review of Published Studies 33 (July 15, 2022).

acetaminophen labels?[16]

2. As of today, does science warrant the addition to acetaminophen labels of any warning or advice regarding in utero exposure to acetaminophen and the risk of ASD or ADHD?

If the United States chooses to respond to this invitation and to declare that the Plaintiffs' proposed label change would result in a misbranding of acetaminophen, then the parties will be given the opportunity to be heard on whether its conclusion preempts any state law claim that such a change to the label is warranted. See Albrecht, 139 S. Ct. at 1679. Until the FDA speaks with more clarity, however, the preemptive force of its views remains unknown.

C. Conflict with NDA-Approved Acetaminophen Products

JJCI makes one final argument in favor of preemption. JJCI notes that some of its acetaminophen products are regulated under NDAs, not monographs. It argues that it would be "absurd" to make labeling changes for monograph-approved acetaminophen

[16] On April 7, 2023, the MDL plaintiffs identified the following Proposed Warning as language that the defendants "could have included on the labels of the acetaminophen products" at issue in this MDL:

> **Autism/ADHD:** Some studies show that frequent use of this product during pregnancy may increase your child's risk of autism and attention deficit hyperactivity disorder. If you use this product during pregnancy to treat your pain and/or fever, use the lowest effective dose for the shortest possible time and at the lowest possible frequency.

when it cannot do so for NDA-approved acetaminophen. It is also premature to decide whether any tension exists between the two regulatory regimes.

When drugs are approved through the NDA process, manufacturers may unilaterally strengthen warnings on labels to reflect "newly acquired information" where there is "sufficient evidence of a causal association" between the drug and the information sought to be added to the label. Utts v. Bristol-Myers Squibb Co., 251 F. Supp. 3d 644, 659-60 (S.D.N.Y. 2017) (citation omitted). The FDA retains the authority, however, to reject labeling changes. Therefore, a manufacturer may show that any proposed labeling change to an NDA-approved drug is preempted where there is "clear evidence that the FDA would not have approved a change" to the label. Wyeth, 555 U.S. at 571.

JJCI argues that there is "clear evidence" that the FDA would not have approved the addition of the warning the Plaintiffs seek here, and therefore the Plaintiffs' proposed labeling change would be preempted if sought for their NDA-approved acetaminophen products. Based on this chain of reasoning, JJCI asserts that it would be an "absurd" result for the Plaintiffs' desired warning to be preempted for its NDA-approved acetaminophen drug products but not for its monograph-approved acetaminophen drug products, and that this tension

between the two drug-approval regimes dictates a finding that the Plaintiffs' claims are preempted.

This last preemption argument also fails. Again, it is brought prematurely. Since JJCI has not proposed any labeling change to the FDA, the FDA has not yet had an opportunity to reject it. Nor has JJCI pointed to an FDA action that demonstrates with sufficient clarity that the FDA would have rejected a change of the kind the Plaintiffs seek here. See Albrecht, 139 S. Ct. at 1679. Until there is a more developed record regarding the FDA's position, it is unnecessary to decide whether there is a mismatch in the regulatory regimes regarding the alleged health risks the Plaintiffs articulate here, and whether that mismatch is sufficient to support a finding of preemption. See Mensing, 564 U.S. at 626 (noting that in drug labeling context, "different federal statutes and regulations may . . . lead to different pre-emption results").

Conclusion

JJCI's February 10, 2023 motion to dismiss the Chapman action on the ground of preemption is denied.

Dated: New York, New York
April 20, 2023

DENISE COTE
United States District Judge