UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Relates To:** *Roberts et al. v. Wal-Mart Stores, Inc.*, No. 22-cv-9012, and *Hatfield et al. v. Wal-Mart Stores, Inc.*, No. 22-cv-9011	**22md3043 (DLC)**

PLAINTIFFS' OMNIBUS OPPOSITION TO DEFENDANT WAL-MART STORES, INC.'S MOTIONS TO DISMISS

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Plaintiffs Lisa Roberts, individually and as mother and guardian of M.M., and Robin Hatfield, individually and as mother and guardian of C.H., submit their Omnibus Opposition to the Motions to Dismiss filed by Defendant Wal-Mart Stores, Inc. ("Walmart").

PRELIMINARY STATEMENT

Ms. Roberts and Ms. Hatfield allege that Walmart violated its duty under Arkansas law to warn them of serious health risks created by Walmart's Equate-brand acetaminophen ("Equate"). An extensive and growing body of peer-reviewed scientific studies shows that prenatal exposure to over-the-counter ("OTC") acetaminophen increases the risk of a child developing autism spectrum disorder ("ASD") and attention-deficit/hyperactivity disorder ("ADHD"). Specifically, acetaminophen exposure causes oxidative stress to a child in utero, which in turn alters brain development. Walmart ignored this risk when it designed the label for Equate.

Ms. Roberts and Ms. Hatfield regularly consumed Equate for minor aches and pains while pregnant with their children. Ms. Roberts's son was diagnosed with ASD at five years old and was also diagnosed with ADHD. Ms. Hatfield's son was diagnosed with ASD at two years old. Both children experience significant behavioral and social difficulties, which has caused immeasurable heartache for their mothers—and significant tangible expenses. Ms. Roberts and Ms. Hatfield had no idea that taking Equate would increase the risk of their children developing ASD and ADHD. Had Walmart warned them, they would have gladly suffered minor aches and pains while pregnant to prevent their children from suffering from a lifelong neurodevelopmental disability.

Walmart seeks to evade Ms. Roberts's and Ms. Hatfield's claims on the threshold legal ground that they are categorically preempted by federal law. According to Walmart, federal law prohibited it from including *any* warning on its label that went beyond the specific, minimum warnings required by FDA. To be clear, Walmart does not, and cannot, argue that any federal law

expressly preempts Plaintiffs' claims. Instead, Walmart argues that Plaintiffs' claims are impliedly preempted because it would have been "impossible" for Walmart to add any warnings to its Equate label that are not already required by FDA.

But Walmart mistakes a floor for a ceiling. Walmart points to regulations requiring Walmart to provide *other* warnings. But the relevant question is not whether federal law sets a floor by requiring Walmart to provide some warnings. Rather, the question is whether federal law also creates a ceiling by *prohibiting* Walmart from including an *additional* warning about ASD and ADHD. Walmart ignores the distinction between a floor and a ceiling because it knows there is no federal law or regulation forbidding the seller of a monograph drug from adding optional warnings on top of the required ones.

It is, therefore, irrelevant to the legal question of preemption when Walmart correctly identifies warnings that are required by the acetaminophen monograph. Those other warnings do not remotely bar Walmart from adding the warnings required by Arkansas law. That point alone is dispositive. In any event, the monograph itself was not binding law until years after Ms. Roberts and Ms. Hatfield took the drug. Because a Tentative Final Monograph ("TFM") does not carry the force of law, courts have repeatedly rejected arguments that such monographs preempt state tort claims. *See, e.g.*, *In re Tylenol (Acetaminophen) Marketing, Sales Practice & Prods. Liab. Litig.*, 144 F. Supp. 3d 699, 712 (E.D. Pa. 2015) ("*In re Tylenol I*"). Walmart commits the same error when it turns from the monograph to the regulation requiring a general pregnancy warning for all OTC drugs. As with the monograph, nothing in that regulation prevented Walmart from including an additional pregnancy warning.

Unable to point to monograph conditions or regulations that prevent additional warnings, Walmart repeatedly relies on inapposite cases and regulations involving drugs covered by the New

Drug Application ("NDA") process. But that regulatory framework is inapplicable to Equate. Marketers of drugs regulated by the NDA system must obtain FDA preapproval for most changes to their applications, including labeling changes. But as FDA itself has said, marketers of drugs regulated by the monograph system do *not* need Agency preapproval to voluntarily supplement their labels. That distinction, which Walmart simply elides, is controlling.

If there were any doubt that acetaminophen marketers are free to supplement the minimum warnings imposed by the monograph system, Walmart's own conduct removes it. The Equate label pasted into Walmart's Motions already contains two warnings not mandated by federal law. Every package of Equate includes a warning about rashes that is not mentioned in the monograph or dictated by FDA regulation. And every package of Equate includes a warning about allergies that not only is not mentioned in the monograph but also was considered unnecessary by FDA. Walmart's position on impossibility preemption therefore reduces to the untenable proposition that it is impossible to do what Walmart is already doing. Walmart's Motions should be denied.

FACTUAL BACKGROUND

In September 2021, over ninety scientists signed a consensus statement published in *Nature Reviews Endocrinology*, a leading peer-reviewed medical journal, calling for precautionary action over the use of acetaminophen during pregnancy. Ann Z. Bauer et al., *Paracetamol Use During Pregnancy—A Call for Precautionary Action*, 17 Nature Revs. Endocrinology 757, 763 (2021). They issued this "call to action" because they could no longer ignore the overwhelming evidence that acetaminophen use during pregnancy could cause ASD and ADHD. *Id.* at 762–63. The authors concluded that "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." *Id*. at 764.

The publication of this consensus statement followed more than a decade of scientific evidence showing that prenatal use of acetaminophen can cause ASD and ADHD. *See generally* Compls. ¶ 32.[1] Since 2013, six European birth cohort studies examining over 70,000 mother-child pairs have shown an association between prenatal use of acetaminophen and ASD and ADHD. *See* Compls. ¶ 33. In total, twenty-six separate epidemiological studies have identified positive associations with acetaminophen exposure during pregnancy and ASD or ADHD. *See* Bauer et al., *supra*, at 762 (collecting studies). Sixteen of those studies specifically investigated whether a dose-response association exists, and they *all* found such an association, meaning increased duration of exposure to acetaminophen was associated with increased risk. *See id*.

The scientific evidence goes beyond standard epidemiological studies. In 2020, a study published in the leading scientific journal *JAMA Psychiatry*, found that umbilical cord "biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD and ASD in a dose-response fashion." Yuelong Ji et al., *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77 JAMA Psychiatry 180, 188 (2020). The study's authors further noted that "[s]ensitivity analyses and subgroup analyses found consistent associations between acetaminophen and ADHD and acetaminophen and ASD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex . . . ." *Id*. at 183. Finally, the authors concluded that their "findings support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk and warrant additional investigations." *Id*. at 188.

[1] Citations designated as "Compls." are to identical allegations in the Roberts and Hatfield Complaints.

Marketers of acetaminophen—like Walmart—have taken no steps to warn pregnant women of these risks. To the contrary, acetaminophen is marketed to pregnant women as the *only* safe over-the-counter option for pain relief on the market. Compls. ¶¶ 15, 38. This is lucrative for the marketers of acetaminophen, as more than 65% women in the United States take the drug during pregnancy. *Id.* ¶ 16. Most of these women do so electively based on the representations of marketers like Walmart that it is a safe pain reliever for pregnant women. *Id.* ¶¶ 17–18.

The prevalence of acetaminophen use during pregnancy has resulted in dire consequences for American children, causing the rates of ASD and ADHD in the United States to skyrocket. In 2002, the Centers for Disease Control and Prevention found that 1 in 68 U.S. children had ASD, which represented a more than 100% increase compared with a decade before. *Id.* ¶ 28. In 2018, the CDC found that 1 in 44 children had been diagnosed with ASD. *Id.* ¶ 27. ADHD likewise impacts many American children, with 8.8% diagnosed with the disorder as of 2019. *Id.* ¶ 29.

The rapid rise in the diagnosis of ASD and the high incidence rate of both ASD and ADHD cannot be accounted for simply by increases in parental awareness and changes in diagnostic criteria. The increasing diagnosis rate has paralleled the increasing market for acetaminophen. The drug was first introduced to the U.S. market in 1955, but its use became more prevalent only after the marketing for acetaminophen was expanded beyond physicians to the general public in 1975. *See id.* ¶ 13. The global market for acetaminophen was $9.44 billion in 2021 and expected to grow to $14.07 billion by 2031. *See Acetaminophen Market to Be Worth US$ 14.07 Billion by the Year 2031 - Comprehensive Research Report by FMI*, Globe News Wire (Mar. 6, 2022), https://www.globenewswire.com/en/news-release/2022/03/07/2397513/0/en/Acetaminophen-Market-to-be-worth-US-14-07-Billion-by-the-year-2031-Comprehensive-Research-Report-by-FMI.html.

Plaintiffs are victims of Walmart's failure to warn of the in-utero risks acetaminophen posed to their children. Walmart makes and sells Equate-brand acetaminophen, Compls. ¶¶ 5, 35, which Ms. Roberts and Ms. Hatfield took during their pregnancies based on the belief that it was safe and with no knowledge that it would cause ASD or ADHD in their children. *Id*. ¶¶ 39–44. While the Equate label warned them of various other risks, including two warnings not required by federal law, nothing on the Equate label alerted them that ingestion of acetaminophen while pregnant could cause ASD or ADHD. *Id*.[2] As a direct result of Walmart's failure to warn them, Ms. Roberts and Ms. Hatfield took acetaminophen while pregnant, which caused their children to develop ASD, *id*. ¶ 76–79, and Ms. Roberts's child to also develop ADHD. Roberts Compl. ¶ 80.

REGULATORY BACKGROUND

FDA provides two regulatory pathways to bring an OTC drug to market: the NDA process and the OTC Drug Review process, also known as the monograph system. Although Walmart recognizes that Equate is regulated by a monograph, Mots. at 11,[3] it consistently conflates the two distinct regulatory systems and builds its preemption argument around concepts that apply only to the NDA process and not to the monograph system. *See, e.g.*, Mots. at 6–8 (relying on a "trilogy" of cases pertaining to the NDA and Abbreviated New Drug Application ("ANDA") process). To ensure that the parties and the Court correctly evaluate the federal regulations—and corresponding preemption arguments—that apply to the monograph system, Plaintiffs provide here an overview of the differences between the NDA process and the monograph system.

[2] *See also* Mots. at 10 (introducing image of Equate label). Plaintiffs agree that the Court may consider the Equate-branded label because it was incorporated into their Complaints by reference. *See Chambers v. Time Warner, Inc.*, 282 F.3d 147, 153 (2d Cir. 2002).

[3] Walmart's Motions to Dismiss the Hatfield and Roberts Complaints are identical, so all citations designated as "Mots." are to both motions. *See* Mem. Br. In Supp. of Mot. to Dismiss for Failure to State a Claim, *Roberts v. Wal-Mart Stores, Inc.*, No. 22-cv-9012 (S.D.N.Y. Sept. 6, 2022), ECF No. 16; Mem. Br. In Supp. of Mot. to Dismiss for Failure to State a Claim, *Hatfield v. Wal-Mart Stores, Inc.*, No. 22-cv-9011 (S.D.N.Y. Sept. 6, 2022), ECF No. 16.

I. The Monograph System Permits Unilateral Label Changes.

The NDA and monograph regulatory schemes differ in many respects, but for present purposes, one distinction is critical: Drug companies have *far more leeway* to change the label of a drug regulated by a monograph than a drug regulated by an NDA or ANDA. ***First***, for NDA drugs, FDA must preapprove nearly all changes to a drug's warning label. For monograph drugs, in contrast, marketers of the drug can make unilateral changes to the warning label that do not conflict with the warnings required by the monograph. ***Second***, the NDA process distinguishes between NDA holders and ANDA holders for purposes of label changes, granting NDA holders the ability in limited situations to change a label pending FDA review but denying ANDA holders even this limited latitude. For monograph drugs that distinction does not matter, as any marketer of the drug may unilaterally add warnings to drugs' labels.

Consider the specifics. The NDA process is highly regulated and requires FDA preapproval of any drug label before a drug can be brought to the market. 21 U.S.C. § 355(a); *see also Guilbeau v. Pfizer Inc.*, 880 F.3d 304, 307 (7th Cir. 2018) (citing 21 U.S.C. § 355(b)(1)) ("The NDA process requires an extensive series of safety and effectiveness trials before a new drug can be sold."). FDA's approval of an NDA before the drug is brought to market includes approval of the *exact text* of the proposed label. *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b). After FDA issues a formal approval letter, a drugmaker may begin marketing the drug using only the exact text from the approved label. And, critically, after that approval occurs, the drugmaker *may not* unilaterally make most types of label changes: "Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application." *Wyeth v. Levine*, 555 U.S. 555, 568 (2009). This stems from 21 C.F.R. § 314.70(b), which prohibits most types of changes to an NDA label without FDA preapproval of a supplemental application.

For NDA drugs, there is an exception to this general rule called the "changes being effected" ("CBE") regulation. 21 C.F.R. § 314.70(c)(6)(iii); *see also Wyeth*, 555 U.S. at 568. Pursuant to the CBE, an NDA holder may unilaterally strengthen the label's warnings and precautions—without FDA preapproval—based on "newly acquired information." 21 C.F.R. § 314.70(c)(6)(iii). FDA can reject the labeling change after the fact if it does not believe the CBE regulation has been satisfied. *Id*. For this reason, preemption analyses of failure to warn claims often turn on (i) whether the drugmaker had amassed "newly acquired information" after FDA's approval of the NDA in question; or (ii) whether, by "clear evidence," FDA would have rejected the labeling change. *See, e.g.*, *Wyeth*, 555 U.S. at 568–72; *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 662–72 (S.D.N.Y. 2017) (Cote, J.), *aff'd sub nom. Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019).

Under the NDA/ANDA system, ANDA manufacturers are not similarly situated with the NDA holder. By regulation that carries the force of law, some manufacturers may gain FDA approval through an ANDA by showing their product matches exactly the product of an NDA holder. But an ANDA holder's warning label must match the NDA holders label *verbatim*. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 613 (2011) ("A manufacturer seeking [ANDA] drug approval, on the other hand, is responsible for ensuring that its warning label is the same as the [NDA]'s.") (citing 21 U.S.C. § 355(j)(2)(A)(v); 355(j)(4)(G); 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7)). So, under the NDA system, ANDA holders *cannot* avail themselves of the CBE regulation to unilaterally strengthen warnings or precautions even in the face of new information. As a result, a state law requiring an ANDA holder to do so is impossible to comply with and thus preempted by federal law. *See Mensing*, 564 U.S. at 618–19; *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 487–88 (2013).

The monograph system is markedly different. Marketers of monograph OTC drugs never submit a premarketing application with a label that FDA approves verbatim. *See* Over-The-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. 13,254, 13,271 (Mar. 17, 1999) ("Products that are marketed under an OTC drug monograph are not required to submit labeling to the agency for preapproval."). Indeed, FDA never approves a monograph drug's label at all. There is *no* regulation akin to 21 C.F.R. § 314.70(b) that requires FDA preapproval to alter an OTC label after a monograph drug is on the market, and thus there is no CBE exception to that nonexistent general rule. *Compare* 21 C.F.R. § 330.1 *with* 21 C.F.R. § 314.70(b). This makes sense because, unlike the NDA system, "the monograph system allows manufacturers to bypass individualized review." *Natural Res. Def. Council, Inc. v. FDA*, 710 F.3d 71, 75 (2d Cir. 2013).

Indeed, that was why FDA established the monograph system in 1972: to efficiently evaluate the safety and effectiveness of hundreds of thousands of OTC drugs that were already on the market. *See In re Tylenol (Acetaminophen) Mktg.*, 2:12-md-02436, 2015 WL 7075949, at *7 (E.D. Pa. Nov. 13, 2015) ("*In re Tylenol II*") ("The monograph system allows for the marketing of OTC drugs containing particular ingredients, which were already on the market before the FDA established the monograph system in 1972."). "Under this system, FDA issues a detailed regulation—a 'monograph'—for each therapeutic class of OTC drug products" and sets forth the conditions under which the drugs are generally recognized as safe and effective. *Natural Res. Def. Council*, 710 F.3d at 75; *see generally* 21 C.F.R. pt. 330 (setting forth regulations applicable to monograph system).

In other words, "[l]ike 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 [generally recognized as safe and effective]." *Natural Res. Def. Council*,

710 F.3d at 75. As the monograph regulatory scheme is premised on regulation by class of drugs, there is no distinction between different brand names (such as Tylenol or Equate)—all are equally situated "marketers" under the applicable regulations. 21 C.F.R. § 330.13(b)(2). No marketer is required to copy the label of another marketer's product, all marketers must comply directly with the monograph, and all marketers may equally supplement the monograph. *See Emley v. Wal-Mart Stores, Inc.*, No. 1:17-CV-2350-WTL-TAB, 2019 WL 2642842, at *8 (S.D. Ind. June 27, 2019) ("*Emley I*") (under federal monograph system, Walmart was permitted to change its Equate label independent of other marketers); *In re Tylenol I*, 144 F. Supp. 3d at 732 n.172 ("While [a different regulation] states that all OTC acetaminophen-based products must contain certain warnings, it does not state that those products cannot contain other warnings. The warnings . . . are a floor, not a ceiling."); *see generally Natural Res. Def. Council*, 710 F.3d at 75; *Canale v. Colgate-Palmolive Co.*, 258 F. Supp. 3d 312, 319 (S.D.N.Y. 2017).

II. The Acetaminophen Monograph Permits Supplementary Warnings.

Consistent with the monograph regulatory scheme, the applicable acetaminophen monograph specifies at the outset that "[a drug like acetaminophen] is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this [monograph] in addition to each of the general conditions established in § 330.1 of this chapter." Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph, 53 Fed. Reg. 46,204, 46,255 ("Acetaminophen Monograph"). The monograph then outlines the applicable conditions. Some are stated in terms of a floor—minimal requirements with no other limitations; others set a ceiling—requirements that cannot be supplemented. For example, with respect to active ingredients, the monograph sets a floor: the active ingredient must "consist of" one of the listed options, including "acetaminophen" and "aspirin." *Id*. If the drug contains one of the listed options, the condition is satisfied. But the

monograph then goes on to set a ceiling—an express limitation—with the condition on "permitted combinations of active ingredients." *Id*. ("Acetaminophen . . . may be combined with *any one ingredient listed below* [under certain conditions]") (emphasis added). This ceiling ensures that acetaminophen is combined with only a discrete number of specified safe ingredients.

The monograph's labeling conditions also set floors and ceilings for the contents of OTC acetaminophen labels like Equate. *See id*. at 46,255–56; *see also* Over the Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. at 13,255 (providing "OTC Drug Product Labeling Outline"). For instance, the "indications" (also known as "uses") condition provides a ceiling: labels may include "*only* the indications for use that have been *established in this paragraph*"—aches and pains, sore throats, headaches, and so on. Acetaminophen Monograph, 53 Fed. Reg. at 46,256 (emphasis added). Thus, if the indications listed on a label went beyond those enumerated indications—suggesting, for instance, that acetaminophen could sooth gout or cure malaria—the label would not comply with the monograph because gout and malaria (unlike sore throat and headache) are not "indications for use that have been established in this paragraph." *Id*.

By contrast, the monograph's "warnings" condition imposes only a floor and not a ceiling. Specifically, the warnings section states that a label satisfies the relevant condition if it "contains the following statements under the headings '[w]arnings.'" *Id*. The monograph then details several such "statements" that the warnings section *must* include. For example, the labels for adult acetaminophen drugs must say: "Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor." *Id*. To the extent the drug is marketed for relief of throat pain, the labels must say: "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly." *Id*.

What the warnings section of the monograph does *not say*, however, is that the required warnings are *exclusive*. That leaves marketers the regulatory freedom to provide *additional,* truthful warnings that do not contradict the warnings required by federal law. Although nothing prevented Walmart from doing so, it did not include on its Equate label any warnings regarding the risk that prenatal ingestion of acetaminophen may cause ASD or ADHD. *See* Mots. at 10.

III. Acetaminophen Was Marketed Under A Tentative Monograph Until Deemed Final By The CARES Act.

A monograph must go through multiple steps before it carries the force of law. As established in 21 C.F.R. § 330.10, the process to a final monograph includes four main steps:

> 1) a review by a panel of qualified experts which then recommend the conditions under which the drug can be used, 2) publication of the expert panel's recommendations in the form of a proposed rule in the Federal Register for public comment, 3) FDA review of the comments on the experts' proposed rule and publication of a tentative final monograph (acetaminophen) with a second opportunity for comments on the TFM, and 4) publication of the final monograph which includes the FDA's findings on when a drug is considered to be generally safe and effective for use.

In re Tylenol II, 2015 WL 7075949, at *8.

On November 16, 1988, FDA reached step three for OTC drugs containing acetaminophen and issued a TFM for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) products, including acetaminophen (*i.e*., the Acetaminophen Monograph). Acetaminophen Monograph, 53 Fed. Reg. at 46,248. For over thirty years, OTC drugs containing acetaminophen operated under the TFM, which had the "legal status . . . of a proposed rule." *Id*. at 46,204.

Congress changed the status of TFMs—including the acetaminophen TFM—with the CARES ACT in March 2020. *See* Coronavirus Aid, Relief, and Economic Security Act, Pub. L. No. 116-136, 134 Stat. 281, 447 (Mar. 27, 2020). It provided that a "tentative final monograph …

shall be deemed to be a final administrative order." *See id*. Accordingly, as of the Act's effective date, September 21, 2021, the tentative monograph for acetaminophen was deemed final. *See* Final Administrative Orders for Over-the-Counter Monographs; Availability, 86 Fed. Reg. 52,474, 52,475–76 (Sept. 21, 2021).

ARGUMENT

Under Arkansas law, Walmart had an obligation to warn Plaintiffs that taking acetaminophen while pregnant could cause their children to develop ASD or ADHD. Walmart contends that it was "impossible to comply with both federal and state law simultaneously," Mots. at 3, but it has not identified any federal law that made it impossible for Walmart to warn Plaintiffs.

"Impossibility pre-emption is a demanding defense." *Wyeth*, 555 U.S. at 573. The Court "start[s] with the assumption that the historic police powers of the States were not to be superseded by [federal law]." *In re Methyl Tertiary Butyl Ether ("MTBE") Prods. Liab. Litig.*, 725 F.3d 65, 96 (2d Cir. 2013) (quoting *Wyeth*, 555 U.S. at 565). To that end, "FDA [has] traditionally regarded state law as a complementary form of drug regulation" and has "long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Wyeth*, 555 U.S. at 78–79. To meet its heavy burden, Walmart must show on the face of the complaint that "it was impossible for it to comply with both federal and state requirements." *Id*. at 573. "If there was *any* available alternative for complying with both federal and state law . . . there is no impossibility preemption." *In re MTBE Prods. Liab. Litig.*, 725 F.3d at 99.

Walmart asserts that it had "no authority to modify the [federally] mandated warning for use during pregnancy." Mots. at 2. But neither of the two sources of federal law on which Walmart relies—(1) the Acetaminophen Monograph and (2) the OTC general pregnancy warning—prevented Walmart from adding to its label the ASD/ADHD warning required by Arkansas law. To the contrary, FDA explicitly provided that—unlike drugs marketed under an NDA or ANDA—

labels for drugs marketed under a monograph could be unilaterally supplemented without FDA approval. Walmart is well aware of this framework. It has unilaterally supplemented its Equate label with at least two warnings *not* included in the applicable federal regulations. Moreover, at the time that Plaintiffs ingested the drug, the Acetaminophen Monograph was not even a federal "law" capable of preempting any state law obligations. For these reasons, neither the Acetaminophen Monograph nor the OTC regulations preempt Walmart's state-law warning obligations, and Walmart's Motions should be denied.

I. The Acetaminophen Monograph Does Not Preempt Plaintiffs' State Law Claims.

A. The monograph permitted Walmart to unilaterally add a warning about the risk of ASD and ADHD if ingested while pregnant.

The label for OTC acetaminophen is regulated by the Acetaminophen Monograph, first as a non-binding proposed rule under the tentative version and then as a regulation with the force of law under the final version. Without any support from the monograph text or applicable authority, Walmart argues that the federal law somehow "forecloses unilateral label changes." Mots. at 13. That is true for most label changes for NDA and ANDA drugs. *See* 21 C.F.R. § 314.70(b) (stating that most changes in labeling for NDA drugs "require[e] supplement submission and approval prior to distribution of the product"). But it is simply not true for drugs governed by the monograph system, like acetaminophen. As FDA has instructed, "[p]roducts that are marketed under an OTC drug monograph are not required to submit labeling to the agency for preapproval." Over-The-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. 13,271. This freedom to act *without* preapproval is the opposite of the regulatory regime that preempts failure-to-warn claims against NDA and ANDA holders. *Cf Bartlett*, 570 U.S. at 472; *Mensing*, 564 U.S. at 604. That fact alone

defeats Walmart's central argument that "[n]either manufacturers nor retailers may . . . supplement FDA's monographs or tentative final monographs." Mots. at 16.[4]

The structure and text of the Acetaminophen Monograph confirm FDA's position. *See N.Y. Currency Res. Corp. v. Commodity Futures Trading Comm'n*, 180 F.3d 83, 92 (2d Cir. 1999) ("Construing a regulation is similar to interpreting a statute; that is, we begin by examining the language."). Specifically, the monograph's warnings section states that a label satisfies the relevant "condition" of the monograph if it "contains the following statements under the headings 'warnings.'" Acetaminophen Monograph, 53 Fed. Reg. at 46,256. The monograph then details several such "statements" that the warnings section *must* include. *Id*.

What the warnings section does *not say*, however, is that the label may not contain *additional* warnings that are required by state law or that the marketer otherwise deems necessary or appropriate. *See Isett v. Aetna Life Ins. Co.*, 947 F.3d 122, 132 (2d Cir. 2020) (declining to read in limitations not included in a regulation's express terms); *Resnik v. Swartz*, 303 F.3d 147, 151–52 (2d Cir. 2002) (explaining that, when particular language is included in one section of a regulation but omitted from another, the omission is presumed to be intentional). Thus, while other aspects of the monograph provide both a floor and a ceiling, *see supra* pp. 10–12, the conditions regarding warnings do not. *Cf. In re Tylenol I*, 144 F. Supp. 3d at 732 n.172 ("While [a different regulation] states that all OTC acetaminophen-based products must contain certain warnings, it does not state that those products cannot contain other warnings. The warnings . . . are a floor, not a ceiling."). Walmart's failure to include such a warning about the risk of ASD

[4] It would also defy logic to allow—indeed, require—NDA holders to unilaterally update their labels through the CBE process when new safety data comes to light but leave marketers of less regulated and less risky OTC drugs regulated by the monograph system with "no process to unilaterally strengthen warnings for use during pregnancy," as Walmart suggests. Mots. at 9.

and ADHD caused by in-utero ingestion of acetaminophen is the result of Walmart's own choice, not any provision in the monograph.[5]

Walmart's failure to understand the applicable regulation permeates its Motions. It insists, for example, that "any entity that departs from the tentative final monograph can face regulatory action," Mots. at 13, that "failure to strictly conform to the tentative final monograph violates FDA requirements," Mots. at 14, and that "any related OTC drug that fails to meet the requirements of the monograph . . . will be recognized as misbranded." Mots. at 15 (quoting FDA Compliance Policy Guide § 450.200). That all dodges the relevant inquiry. What the monograph "require[s]" is that the warnings section of the label must include the specific warnings listed. Plaintiffs agree that *failing* to include the *required* warnings would indeed violate the monograph. For example, if the Equate label failed to say that "[p]rompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms," then it would indeed "fail[] to meet the requirements of the monograph" because the monograph *requires* that statement. *See* Acetaminophen Monograph, 53 Fed. Reg. at 46,256. But because the monograph nowhere *forbids* a drug company from including *additional* warnings once it has already included the required ones, Walmart would not have been "depart[ing] from," "fail[ing] to strictly conform to," or "fail[ing] to meet the requirements of" the monograph, Mots. at 13, 14, 15, if it had included the additional warning about ASD and ADHD required by Arkansas law.

This is also why Walmart is misguided in relying on the monograph's requirement that aspirin labels say, "do not take this product during the last 3 months of pregnancy." Mots. at 15

[5] Setting a floor for warnings, as opposed to the ceiling set for uses/indications, makes sense. FDA has good reason to limit what uses OTC drug makers may list for their products: a drug maker has every incentive to make the uses section as broad as possible to increase overall use and sales, necessitating a ceiling on what uses may appear in the label. But for warnings, the incentives are reversed. Given the adverse business effects that come from additional warnings, a drug maker would have no reason to include inappropriate warnings, thus necessitating a floor but not a ceiling.

(citing Acetaminophen Monograph, 53 Fed. Reg. at 46,245). This required warning is just another floor for a different drug. There is nothing in the monograph that would forbid the makers of aspirin from including warnings *in addition to* the warning about the last three months of pregnancy. And there is likewise nothing in the monograph that forbade Walmart from adding a warning about ASD to its Equate label so long as Walmart also included the warnings that the monograph requires.

Walmart's conflation of regulatory regimes also leads it to rely on processes and distinctions relevant only under the NDA/ANDA scheme. For example, Walmart argues that its status as a "retailer" somehow means that it could not change its Equate labels. Mots. at 20–24. Even if that argument did not directly contradict to allegations of the complaint,[6] it is a distinction without significance under the monograph system, which applies to all marketers of OTC acetaminophen alike, with no distinctions in the regulations or case law for different brands of marketers. *See generally* 21 C.F.R. pt. 330. Walmart's argument that there is "clear evidence" that FDA would reject label changes is equally irrelevant, Mots. at II.B., as the "clear evidence" standard is applicable only to label changes through the CBE process under the NDA/ANDA regulations. *Compare* 21 C.F.R. § 330.1 (setting forth "conditions for general recognition [of over-the-counter drugs] as . . . not misbranded") *with* 21 C.F.R. § 314.70(b) (setting forth stringent requirements for label changes to drugs approved under the NDA process). There is no need to speculate about new information or FDA's hypothetical approval when such information is inapplicable under the monograph. For this reason, Walmart's cases involving FDA guidance to

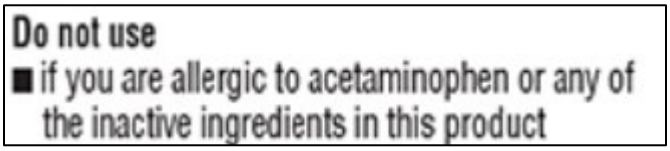
[6] For purposes of Walmart's Motion, the Court should accept as true the well-pleaded allegations that, at all relevant times, Walmart "was engaged in the business of manufacturing and selling the [acetaminophen] in the United States." Compls. ¶ 35; *see also* Roberts Compl. ¶ 60, Hatfield Compl. ¶ 58 ("At all relevant times, Defendant engaged in the business of testing, developing, designing, manufacturing, marketing, labeling, selling, distributing, and promoting [acetaminophen].").

NDA/ANDA holders have no bearing here. *See, e.g.*, *Gaeta v. Perrigo Pharms. Co.*, 562 F. Supp. 2d 1091, 1098 (N.D. Cal. 2008) ("Since including these warning[s] would put the [defendant's] ANDA in jeopardy for failing to conform with the FDA's approved labeling for the listed drug, [p]laintiffs' state law causes of action conflict with [defendant's] obligations under federal law.")

B. Walmart's current label includes warnings not in the monograph.

If there were any doubt about Walmart's ability to unilaterally add additional warnings not required by the monograph, Walmart's own conduct dispels it. Walmart's Equate label, as included in its Motion, *already includes two additional warnings that are not mentioned in the monograph*. It would be hard to identify clearer evidence that it was not impossible for Walmart to include additional warnings not mentioned in the monograph—Walmart has already done so. *Cf. In re Tylenol I*, 144 F. Supp. 3d at 730 ("Despite the defendants' insistence that changing the Extra Strength Tylenol label would be impossible, they have already done it."); *id*. at 730 n.169 (holding that the fact that a defendant "voluntarily changed the label" "can be used to rebut the defendants' defense of impossibility"). And it has done so with FDA's blessing.

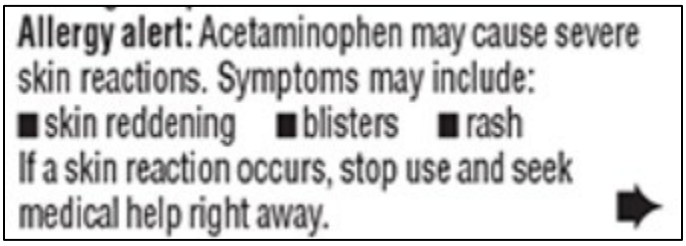
First, the Equate label warns, "Do not use . . . if you are allergic to acetaminophen or any of the inactive ingredients in this product."



Mots. at 10. The monograph does not require this warning. *See* Acetaminophen Monograph, 53 Fed. Reg. at 46,256–57. In fact, the first part of this warning—about not using acetaminophen if allergic to it—was specifically considered and rejected by FDA. *See id*. at 46,218 ("[S]everal comments . . . recommended a label warning to advise consumers who are allergic to

acetaminophen not to use products containing that drug . . . . The agency believes that the warnings . . . are not warranted at this time because there is insufficient evidence that these adverse effects are being caused by acetaminophen."). And the second part of the warning—about inactive ingredients—simply does not appear in the monograph at all.

Second, the Equate label also warns that "acetaminophen may cause severe skin reactions" whose "symptoms may include skin reddening . . . blisters . . . [and] rash."



Mots. at 10. This warning also is not required by the monograph.

Although there is informal FDA guidance providing that drug companies *may* include a rash warning without risk of being prosecuted for misbranding,[7] that guidance does not carry the force of law.[8] If the monograph did prohibit the inclusion of additional warnings, informal FDA guidance could not override that legal requirement. Indeed, FDA's guidance confirms that FDA does not view the monograph as a ceiling: FDA could not recommend that marketers voluntarily add a skin rash warning if the monograph forbade them from adding such a warning. Thus, the

[7] FDA, *Guidance for Industry: Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions* (Jan. 2017), *available at* https://www.fda.gov/media/90572/download.

[8] *Id.* ("This guidance represents the current thinking of the [FDA] on this topic. It does not establish any rights for any person and is not binding on FDA or the public."); *see also Hearing on Modernizing FDA's Regulation of Over-the-Counter Drugs Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 115th Cong. 9 (2017) (statement of Janet Woodcock, Director, Center for Drug Evaluation & Research, Food & Drug Administration), *available at* https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Woodcock-HE-Hrg-on-Modernizing-FDA%E2%80% 99s-Regulation-of-Over-the-Counter-Drugs-09-13-17.pdf ("In order to more quickly encourage appropriate labeling changes, the Agency opted to issue a guidance instead, requesting that manufacturers add a warning to their labels.").

inclusion of the skin-rash warning—with FDA's blessing and despite its absence in the list of required warnings in the monograph—demonstrates that the monograph warnings section merely provides the floor, a list of warnings that *must* be included on the label but does not preclude *additional* warnings.

The Equate label also includes "other information" that the monograph nowhere mentions. Specifically, the Equate label says, "store at 22° C (77°F); excursions permitted between 15°-30°C (59°-86°F)" and says, "see end flap for expiration date and lot number."


Other information
- store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F)
- see end flap for expiration date and lot number

Mots. at 10. These two pieces of information are similarly not required by the monograph, demonstrating (once again) that the monograph provides a floor rather than a ceiling.

C. The Acetaminophen Monograph could not preempt state law warning obligations before September 21, 2020, because it did not have the force of law.

In addition to permitting Walmart to include the pregnancy warnings required by state law, the Acetaminophen Monograph also leaves these Plaintiffs' state law claims unaffected because it was not binding "law" of the United States at the time relevant to these claims. U.S. Const. Art. vi, Cl.2. Only "agency action carrying the force of law"—not tentative agency pronouncements, proposed rules, or FDA guidance—can preempt state law. *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1679 (2019); *see id*. at 1683 (Thomas, J., concurring) ("[T]he [FDA] letter was not a final agency action with the force of law, so it cannot be 'Law' with pre-emptive effect."); *Wyeth*, 555 U.S. at 576. There is no question that, prior to September 21, 2021, the Acetaminophen Monograph had the "legal status . . . of a proposed rule." Acetaminophen

Monograph, 53 Fed. Reg. at 46,204. Therefore, it was not binding until deemed final by the CARES Act. *See* Final Administrative Orders for Over-the-Counter Monographs; Availability, 86 Fed. Reg. 52,465–66; Acetaminophen Monograph, 53 Fed. Reg. at 46,204 ("Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products."). Before that time, including at the time these Plaintiffs ingested the drug, *see* Roberts Compl. ¶ 39; Hatfield Compl. ¶ 39–40, Walmart "market[ed] products at their own risk and [was] able to make voluntary adjustments [to its' product labels] taking into account the information presented in the proposed TFM." *In re Tylenol I*, 144 F. Supp. 3d at 731 (quoting FDA Letter re: FOIA Request, Nov. 17, 2011). There was simply "no applicable provision that provide[d] for regulatory action for the failure to conform to [the] tentative final monograph." *Emley I*, 2019 WL 2642842, at *5.[9]

Because TFMs do not carry the force of law, courts across the country have rejected arguments that they preempt state law claims. *See, e.g.*, *Macormic v. Vi-jon, LLC*, No. 4:20CV1267 HEA, 2021 WL 6119166, at *8 (E.D. Mo. Aug. 6, 2021) (finding no conflict preemption because a TFM "was never adopted and has the legal status of only a proposed rule"); *Won Kyung Hwang v. Ohso Clean, Inc.*, No. C-12-06355 JCS, 2013 WL 1632697, at *17 (N.D. Cal. Apr. 16, 2013) (declining to find state-law claim preempted because the TFM only has the status of a proposed rule); *Emley I*, 2019 WL 2642842, at *5 ("A tentative final monograph has no 'effective date,' because it is simply a proposed rule. By its very terms, the tentative final

[9] The non-binding nature of the TFM is also clear from the finalization timeline. Section 330.10(b) provides that "[a]ny product which fails to conform to an applicable monograph *after its effective date* is liable to regulatory action." 21 C.F.R. § 330.10(b) (emphasis added). Only a truly final monograph, and not a tentative final monograph, has an "effective date." *See* 21 C.F.R. § 330.10(a)(9). And the monograph at issue here did not have an effective date until September 2021. *See* 86 Fed. Reg. 52474-01, at 52465-66, 2021 WL 4263226 (Sept. 21, 2021).

monograph does not have the force of law; therefore, the Defendants cannot be in violation of federal law by failing to comply with it."); *Emley v. Wal-Mart Stores, Inc.*, 2020 WL 509172, at *4 (S.D. Ind. Jan. 31, 2020) (denying motion for reconsideration and explaining that "FDA did not rely on the tentative final monograph to initiate action against a manufacturer, relying instead on codified warnings that were separate and distinct from the tentative final monograph"). That is correct as a matter of basic administrative law, and this Court should conclude the same here.

In its attempt to circumvent the non-binding nature of the TFM, Walmart musters only four out-of-circuit district court cases. *See* Mots. at 13 (citing *Harris v. Topco Assocs., LLC*, 538 F. Supp. 3d 826, 832 (N.D. Ill. 2021); *Bailey v. Rite Aid Corp.*, No. 18-cv-06926, 2019 WL 4260394, at *4 (N.D. Cal. Sept. 9, 2019); and *United States v. Vita-Erb, Ltd.*, No. 05-3494-CV, 2006 WL 3313941, at *6 (W.D. Mo. Nov. 14, 2006)); Mots. at 14 (citing *Hartwich v. Kroger Co.*, No. 8:20-cv-01253, 2021 WL 4519019, at *4 (C.D. Cal. Sept. 20, 2021)). But none of these cases held that a tentative final monograph preempts a state-law tort claim on impossibility-preemption grounds. In *Bailey*, the court ultimately held that "plaintiff's claims [were] *not* preempted by any federal regulation," so its statements about the legal effect of tentative monographs are dicta. 2019 WL 4260394, at *4 (emphasis added). In *Harris*, the court analyzed express, not implied, preemption under 21 U.S.C. § 379r(a)—a federal-law provision that Walmart does not invoke here. 538 F. Supp. at 830. And the remaining two cases—*Hartwich* and *Vita-Erb*—are not preemption cases at all. To the extent these out-of-circuit district-court cases suggested that a tentative final monograph carries the force of law while it is still tentative, the cases are mistaken. FDA has made clear that a TFM is a "*proposed* rule." Acetaminophen Monograph, 53 Fed. Reg. 46,204 (emphasis added). And proposed rules cannot preempt state law. *See Albrecht*, 139 S. Ct. at 1679; *Wyeth*, 555 U.S. at 576.

II. The OTC General Pregnancy Warning Does Not Preempt Plaintiffs' State Law Claims.

In addition to the applicable monograph, acetaminophen is regulated by the general federal regulations for OTC drug labeling, including the general pregnancy warning found in 21 C.F.R. § 201.63(a).[10] There is no dispute that Walmart was required to include that warning on its label. Indeed, Plaintiffs agree with most of Walmart's statements about that regulation:

- "The use during pregnancy warning mandated by codified regulations applies to over-the-counter acetaminophen." Mots. at 11 (citation and internal quotation marks omitted).[11]
- "[T]his warning must be located under the heading Warning or Warnings, and the first four words of this statement must be in bold type." *Id*.
- "Nothing in the tentative final monograph contradicts FDA's general use-during-pregnancy warning for acetaminophen products." *Id*. at 11.
- "Neither an NDA or a monograph changed the [general pregnancy] warning or provided a different one. And there is no other means for changing the [general] pregnancy warning unilaterally." *Id*. at 12–13.
- "Plaintiffs do not allege that Walmart's Equate-branded acetaminophen products ever violated this regulation." *Id*. at 9.
- "Plaintiffs do not allege that over-the-counter acetaminophen products have been exempted from this regulation." *Id*. at 11.
- "Nor do Plaintiffs allege that either an NDA or final monograph imposes a more specific warning with which an Equate-branded acetaminophen product failed to comply." *Id*.

These statements are correct but irrelevant. What Walmart gets wrong is the assertion underlying its entire preemption argument: "Neither the manufacturer for Equate-branded acetaminophen nor Walmart has any authority to change [the general pregnancy] warnings *or impose new ones*." *Id*. at 1 (emphasis added). To the contrary, while Walmart was not permitted to unilaterally change

[10] Walmart asserts that the general pregnancy warning is required by the monograph, but Walmart mistakenly cites comments on the monograph, rather than the monograph itself, which relate to aspirin, not acetaminophen. Mots. at 14. To be clear, although the general pregnancy warning with respect to acetaminophen is not directly incorporated into the monograph, Plaintiffs agree that Walmart must comply with its warning obligations under both the monograph and the OTC labeling regulations, along with all state law warning obligations consistent with these federal warnings. *See generally* 21 C.F.R. § 343.1 (incorporating § 330.1, which itself incorporates § 201.63).

[11] Citations and internal quotations marks are omitted throughout this list.

or contradict the language of the general pregnancy warning, just as with the monograph, nothing in the OTC regulations prevented Walmart from including *additional* warnings required by state law. *See Isett*, 947 F.3d at 132; *Resnik*, 303 F.3d at 152.

The text of the general pregnancy warning regulation confirms the point:

> 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). While the word "shall" in the regulation "indicates a command" to include the general pregnancy warning unless "specifically exempted," *United States v. Kahn*, 5 F.4th 167, 174 (2d Cir. 2021), it does not indicate any prohibition on warnings required by state law.

Likewise, the exception established by this regulation—which Walmart selectively quotes—contains no restrictions on additional warnings:

> 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.

21 C.F.R. § 201.63. Thus, an OTC marketer can *replace* the required general warning—*i.e.*, use a different warning "in place of" it—only when a different warning is specified in an NDA or final monograph. But again, nothing precludes an OTC marketer of a drug subject to a tentative final monograph, or even a final monograph, from including additional warnings.

To the contrary, FDA specifically contemplated that marketers of OTC drugs would add voluntary warnings without FDA preapproval. In 1999, FDA responded to comments on the

format and content requirements for OTC drugs, including § 201.63, about voluntary warnings. At the time, OTC manufacturers were concerned that placing voluntary warnings "outside of the [regulated] headings could create the impression that these warnings are less or more important than the required warnings." Over-The-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. at 13,271. In response, FDA made clear that "voluntary warnings to OTC products" were not only permitted but encouraged: "FDA agrees that consumers may be confused if an appropriate warning were placed outside of the Drug Facts area. Thus, the agency expects such warnings to appear under the 'Warnings' heading, preceded by an appropriate subheading." *Id*.

FDA likewise made its intent clear by declining to finalize proposed provisions that would have preempted some state law obligations. Instead, FDA deferred to Congress, which, through amendment of the Food and Drug Administration Modernization Act, specified that federal OTC drug labeling requirements do not "modify or otherwise affect any action or the liability of any person under the product liability law of any State." 21 U.S.C. 379r(e); *see also Wyeth*, 555 U.S. at 575 n.8 (noting Congress' express preservation of product liability actions for OTC drugs).

In sum, Walmart selectively quotes from a regulation that (1) requires all OTC medications to include a general pregnancy warning and (2) says that this required warning can be *replaced* only if authorized by another law. But neither of these requirements prohibits Walmart from adding a warning specific to ASD and ADHD risks, as FDA itself recognized.

CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court deny Walmart's Motions.

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Respectfully submitted,

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