Over-the-Counter Products

Is Implied Preemption a Viable Defense?

By Richard A. Dean, K. Michele Anderson, and Corena G. Larimer

Mounting the defense involves understanding the monograph drug world and how existing preemption principles translate to it.

Courts have issued many preemption decisions involving brand-name and generic drugs in recent years, but only a handful involved over-the-counter products. Preemption of claims involving over-the-counter (OTC) products is a complicated area generally, made much more so by the different regulatory avenues to market and numerous detailed regulations specific to particular drug substances or categories of drugs. This article provides an overview of implied preemption in the world of OTC products.

The first section discusses the component parts of OTC regulation and includes an overview of key provisions that can affect preemption. The second section outlines the general principles that frame the conflict preemption analysis for all drugs. The third section extensively discusses the OTC monograph process, a unique, and to many, unfamiliar process that gives rise to a preemption defense that differs from the defenses available for products that come to market through the traditional New Drug Application or Abbreviated New Drug Application processes. Finally, the last section discusses several regulations that impose specific and detailed labeling requirements for all OTC products. Viewed through the lens of preemption jurisprudence that has developed in recent years, these regulations can form the foundation of an important preemption defense to product liability lawsuits.

OTC Drugs: An Overview

There are three regulatory pathways by which an OTC product can be marketed. Two are familiar to those who work with prescription pharmaceuticals: the traditional New Drug Application (NDA) process, and for generic products, the Abbreviated New Drug Application (ANDA) process. *See, e.g., In re Tylenol (Acetaminophen) Mktg., Sales Practices &*

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Prods. Liab. Litig., 144 F. Supp. 3d 699, 708–09 (E.D. Pa. 2015) (noting that Extra Strength Tylenol was regulated at times by a monograph and at times by an NDA); *Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454, 455–56, 458 (D.D.C. 1999). The third pathway is the monograph process, which is unique to OTC products. *Cutler v. Kennedy*, 475 F. Supp. 838, 844–46 (D.D.C. 1979); *Mills v. Warner-Lambert Co.*, 581 F. Supp. 2d 772, 783–84 (E.D. Tex. 2008); 21 C.F.R. §330.10; *see also* Consumer Healthcare Products Association, Your Health at Hand Book: Guide to OTC Active Ingredients in the United States – Supplement to *Pharmacy Today* (Oct. 2010), http://www.yourhealthathand.org.

Congress exempted product liability tort lawsuits from the express preemption provision that it enacted for OTC drugs generally, 21 U.S.C. §379r(e). But the Supreme Court is clear that "the absence of express pre-emption is not a reason to find no *conflict* pre-emption."

These different pathways are critical when analyzing preemption arguments for an OTC product. The mechanism for modifying an NDA or ANDA drug or its label, and the impossibility-preemption arguments that follow, are discussed in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), *Wyeth v. Levine*, 555 U.S. 555 (2009), and *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013), and a spate of lower court rulings that followed, though a drug's OTC status can present additional nuances. An OTC drug marketed under a monograph, however, cannot be modified or relabeled using the mechanisms prescribed for NDA or ANDA drugs. Changes for monograph OTC drugs are subject to different restrictions, and those monograph-specific constraints can be crucial to an impossibility-preemption defense.

The U.S. Food and Drug Administration (FDA) has also created detailed regulations that govern labeling across all OTC products, regardless of a drug's avenue to market. The most prominent is the Drug Facts Rule, 21 C.F.R. §201.66, which provides standardized content and format requirements for all OTC products. The FDA also enacted numerous product-specific requirements in its regulations, which are incorporated into the Drug Facts Rule's labeling requirements, either individually or under a catch-all provision. *See* 21 C.F.R. 300 *et seq.*; 21 C.F.R. §201.66(c)(5)(ii), (viii). For example, 21 C.F.R. §201.310 provides language for products containing phenindione; section 201.325 does likewise for OTC vaginal contraceptives containing nonoxynol-9 as an active ingredient; and section 201.326 does the same for products with internal analgesics or antipyretics, such as acetaminophen, aspirin, ibuprofen, and others. Regulations such as these can play a critical role in a company's preemption defense, if the facts of a particular case or claim implicate their FDA-imposed requirements.

General Preemption Principles

Federal preemption can arise from an express statutory preemption clause, or it can be implied from statutory and regulatory context. Congress exempted product liability tort lawsuits from the express preemption provision that it enacted for OTC drugs generally, 21 U.S.C. §379r(e). But the Supreme Court is clear that "the absence of express pre-emption is not a reason to find no *conflict* pre-emption." *Mensing*, 564 U.S. at 618 n.5. And implied conflict preemption may present a powerful defense for some OTC drugs.

Impossibility preemption—a form of implied preemption—is controlled by the Supreme Court's decisions in *Wyeth* and *Mensing*. These cases clarified that impossibility preemption asks (1) "whether the private party could independently do under federal law what state law requires of it," and (2) if independent action were possible, whether "clear evidence" shows that the FDA would have rejected such action after the fact. *Mensing*, 564 U.S. at 620; *Wyeth*, 555 U.S. at 573. A defendant may establish preemption under either prong.

In *Mensing*, the Court recognized that a generic prescription drug must bear the same label as the corresponding brand-name drug and that the generic drug's manufacturer could not change the label without the FDA's permission. That fact—that the manufacturer could not unilaterally or independently comply with the alleged state law duty—was sufficient to establish preemption. *Mensing*, 564 U.S. at 618, 623–624. *Mensing* distinguished *Wyeth*, in which the Supreme Court rejected preemption when the manufacturer of a brand-name drug could have unilaterally changed its label to fulfill a purported state law duty. The Court ruled against impossibility preemption under those circumstances, except when clear evidence shows that the FDA would have later rejected the change. *Wyeth*, 555 U.S. at 568.

The differing results in *Mensing* and *Wyeth* stem from the availability, under federal law, of the Changes Being Effected (CBE) process, which allows a company to implement certain label changes without prior FDA approval of the change; federal law made the CBE process available for the brand-name drug in *Wyeth* but not for the generic drug in *Mensing*. *Mensing*, 564 U.S. at 624; *see also id.* at 614 ("When making labeling changes using the CBE process, drug manufacturers need not wait for preapproval by the FDA, which ordinarily is necessary to change a label."); *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 37 (1st Cir. 2015) (further explaining the CBE and prior approval procedures under 21 C.F.R. §314.70(c)(6)(iii) and §314.70(b)(2)(v)(A), respectively).

The Supreme Court stated *Mensing*'s preemption rule in general terms, and many courts have since recognized that the framework extends well beyond the context of generic drugs. For example, the Sixth Circuit applied the *Mensing* doctrine to design-defect claims involving a brand-name drug, finding them preempted because the manufacturer would

have had to submit a request to the FDA before changing the design of its drug. *Yates v. Ortho-McNeil-Janssen Pharm., Inc.*, 808 F.3d 281, 298–300 (6th Cir. 2015). Other courts have similarly recognized that the same preemption framework applies outside of *Mensing*'s particular facts, and even outside of the pharmaceutical context entirely. *E.g., Sikkelee v. Precision Airmotive Corp.*, 822 F.3d 680, 703–704 (3d Cir. 2016), *cert. denied sub nom. AVCO Corp. v. Sikkelee*, 137 S. Ct. 495 (2016) (involving federal aviation regulations); *Aston v. Johnson & Johnson*, ___ F. Supp. 3d ___, 2017 WL 1214399 (D.D.C. Mar. 31, 2017); *Utts v. Bristol-Myers Squibb Co.*, 226 F. Supp. 3d. 166, 185–86 (S.D.N.Y. 2016); *In re Lipitor Marketing, Sales Practices & Prods. Liab. Litig.*, 185 F. Supp. 3d 761, 768–69 (D.S.C. 2016); *Fleming v. Janssen Pharm., Inc.*, 186 F. Supp. 3d 826, 833–34 (W.D. Tenn. 2016).

In short, impossibility preemption may be triggered wherever a company—including the manufacturer of an OTC drug—must obtain federal permission or approval before it can comply with a purported state law duty.

A Preemption Defense for Monograph Products

Developing a preemption defense for monograph products requires understanding how the monograph process came about, how a monograph is established, what steps are necessary to revise a final monograph, and the general labeling requirements for OTC monograph products. With that understanding, attorneys will be able to apply the preemption principles that have developed in other contexts to the world of OTC products.

How Did the Monograph Process Come About?

Congress passed the Drug Amendments Act in 1962, establishing "effectiveness" as a requirement for new drugs and charging the FDA with reviewing the efficacy of all drugs—prescription and OTC—then on the market. The FDA, concluding that a drug-by-drug review of the hundreds of thousands of existing OTC drugs was unworkable, later retained the National Academy of Sciences National Research Council to assist in creating advisory panels of outside experts to review the existing OTC drugs. *See Mills*, 581 F. Supp. 2d at 783–84; *Weinberger v. Bentex Pharm.*, 412 U.S. 645, 651 (1973). Rather than undertake individual reviews, the expert panels reviewed 26 categories, including 88 subgroups, of OTC drugs.

These advisory panels were then charged with developing proposed monographs, which would establish the conditions for marketing a drug without an NDA. *Mills*, 581 F. Supp. 2d at 783–84. The overarching standards that the panels and the FDA apply to a monograph label include that the monograph be "clear and truthful in all respects"; contain instructions, warnings, and other specific categories of information; and be written "in such terms as to render [the labeling] likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use." 21 C.F.R. §330.10(a)(4)(v).

How Is a Monograph Established?

The monograph process has four general stages:

1. The FDA's expert advisory panel reviews existing data to determine whether and under which conditions a drug can be marketed without an NDA. The panel issues its recommendations as a proposed monograph.
2. The FDA reviews the proposed monograph and publishes it in the Federal Register for public comment.
3. After reviewing the comments on the proposed monograph, the FDA publishes a tentative final monograph (TFM) and again allows comments and the opportunity for formal objections to its findings.
4. After the comment period ends, the FDA issues a final monograph with "conclusive and legally binding determinations on the conditions under which a drug is considered generally safe and effective for use." *Mills*, 581 F. Supp. 2d at 784. The monograph is published as an agency regulation in the Code of Federal Regulations.

21 C.F.R. §330.10(a)(1)–(9); *see also Mills*, 581 F. Supp. 2d at 783–84; *Cutler v Hayes*, 818 F.2d 879, 884 (D.C. Cir. 1987). With certain restrictions, an OTC product may be sold while this process—which spans years, and even decades—is ongoing. *See, e.g.,* 21 C.F.R. §330.13.

Approximately 125 final monographs had been issued by 2010. *Nat'l Res. Defense Council, Inc. v. FDA*, 710 F.3d 71, 75 (2d Cir. 2013). Many of these monographs can be found in part 300 of the Code of Federal Regulations. *See* 21 C.F.R. §331.1 *et seq.*

Impossibility

preemption may be triggered wherever a company—including the manufacturer of an OTC drug—must obtain federal permission or approval before it can comply with a purported state law duty.

How Can a Final Monograph Be Changed?

Once a final monograph for a category of OTC products takes effect, there are only three ways to modify it: (1) the FDA may propose to amend or repeal the monograph; (2) an interested party may submit a Citizen's Petition; or (3) a company may submit an NDA, which the FDA treats as a petition to amend the monograph under certain circumstances. 21 C.F.R. §330.10(a)(12). The monograph process is not subject to the CBE mechanism outlined in 21 C.F.R. §314.70 because the regulation allows changes only to an "approved NDA," and a final monograph is not an approved "application" or NDA. 21 C.F.R. §314.3 ("Application… is the application described under §314.50"); 21 C.F.R. §314.50. The unavailability of the CBE or a similar process to amend a final monograph without FDA approval and rulemaking reflects the formal, deliberative process required to create and finalize the monograph in the first instance.

What Are the General Labeling Requirements for OTC Monograph Products?

It is illegal to sell an OTC monograph product that does not conform to the applicable monograph. 21 U.S.C. §§331–334. The monograph process establishes specific and detailed requirements for the products marketed under a particular monograph.

When state law would require warnings that the manufacturer cannot implement without FDA permission or assistance, that duty is preempted.

See 21 C.F.R. §330.1. Many monographs and other OTC regulations contain label language in quotation marks; that language must be included exactly as written in a monograph product's label. 21 C.F.R. §330.1(c)(2). Even for monograph language that is not designated as "exact language" by quotation marks, conformity is required: "[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).

In addition to the language dictated by a particular monograph, the FDA has enacted a number of labeling requirements that apply to specific active ingredients or certain categories of drugs. *See, e.g.,* 21 C.F.R. §369.21 (warning and caution statements required for various drugs and compounds); 21 C.F.R. §201.326 (organ-specific warnings for OTC internal analgesics and related drugs); 21 C.F.R. §201.327 (detailed labeling for OTC sunscreen products). Many of these requirements apply to all OTC products, whether marketed under a monograph, NDA, or ANDA.

Applying Preemption Principles to the Monograph World

With this background, the key preemption question is whether the manufacturer of a product regulated under a monograph must obtain FDA approval to include a warning or other language in its label that departs from the monograph. When state law would require warnings that the manufacturer cannot implement without FDA permission or assistance, that duty is preempted. *Mensing*, 564 U.S. at 623–24.

Can a Product's Label Deviate from a Final Monograph?

Final monographs provide the most clear-cut foundation for a preemption defense. When a monograph or other OTC regulation requires specific label language, (*e.g.,* 21 C.F.R. §330.1(c)(2), 21 C.F.R. §369.21), the preemption analysis appears straightforward. The "exact language" requirement is similar to the one in *Mensing*—a private party is obligated to use language required by the FDA—and any state law claim that the language should have differed is in unmistakable conflict with federal requirements. Even for claims that do not implicate "exact language" listed in the monograph, without an exemption from the FDA, a manufacturer must maintain conformity with the final monograph; if it does not, sale of its product is illegal, and it is subject to regulatory action. 21 C.F.R. §§330.1, 330.10(b).

The FDA explicitly rejected requests for "flexibility" in crafting warnings for monograph products, explaining that "consistently worded warnings are essential to the safe use of an OTC drug product and that permitting flexibility in this section of the labeling could put consumers at risk." Labeling of Drug Products for Over-the-Counter Human Use, 51 Fed. Reg. 16,258-01, 16,263 (May 1, 1986). Instead, "the exact wording of warnings in an OTC drug monograph will continue to be required." *Id.*

Further, a manufacturer has no apparent avenue for implementing a label change independently, as is required to avoid preemption under *Mensing*. The final monograph itself cannot be changed without formal FDA rulemaking, as discussed above, and the monograph regulations do not provide manufacturers with a mechanism to change a particular product's labeling unilaterally, as the CBE procedure does for manufacturers of NDA products. *See, e.g.*, *In re Tylenol*, 144 F. Supp. 3d at 729–30; 21 C.F.R. §314.70(c)(6) (permitting CBE procedure for "an approved NDA").

Instead, the regulations allow a manufacturer to file a limited New Drug Application that requests approval for an OTC drug "deviating in any respect from a monograph that has become final." 21 C.F.R. §330.11; *see also* Over-The-Counter Drug Monograph System—Past, Present, and Future; Public Hearing, 79 Fed. Reg. 10,168-01, 10,171 (Feb. 24, 2014) (explaining, as an example, that a manufacturer wishing to use a dosage form not included in the monograph could submit an NDA relying largely on the monograph and providing information limited to showing safety and efficacy of the new dosage form). And although the FDA has suggested—but not in regulations—that "[p]roducts that are marketed under an OTC drug monograph are not required to submit labeling to the agency for preapproval," that statement was made in the context of, and is arguably limited to, how manufacturers could implement the content and formatting requirements of the Drug Facts Rule when it first took effect. *See* Over-The-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. 13,254-01, 13,271 (Mar. 17, 1999).

Even if a pathway to change the label independently did exist, it would not excuse the conformity requirement. 21 C.F.R. §§330.1(c), 330.10(b). The FDA has a policy of forbearing from legal action when an OTC product label adds "warning, contraindication, side effects, and/or precaution information" to labeling before a final monograph takes effect. 21 C.F.R. §330.12(d)(1). But that policy's "comfort" does not extend to products governed by a final monograph. 21 C.F.R. §330.12(e) ("At such time as an applicable OTC drug monograph becomes effective,… any appropriate regulatory action will be initiated."). The FDA has repeatedly explained in warning letters that manufacturers must either relabel their products to conform to a final monograph once it takes effect, or alternatively, they must submit an NDA to obtain FDA approval of any deviations. *See, e.g.,* Letter from Joseph Matrisciano, Jr., Director, New England District Office, U.S. Food and Drug Admin., to Andrea F. Sama, Plant Manager, Aplicare Inc. (Dec. 15, 2016). Indeed, the FDA has threatened legal action when a product's label did not conform to

the applicable final monograph. *See, e.g., id*. This regulatory enforcement against manufacturers for "deviating" from a final monograph demonstrates that manufacturers' hands are tied; they must obtain prior FDA approval before they can safely take action to amend product labeling.

Because federal law leaves manufacturers of OTC products that are governed by a final monograph unable to change warnings or other safety information unilaterally, related state tort claims are subject to preemption under *Mensing*. This defense appears untested; there does not appear to be post-*Mensing* case law squarely confronting this issue for an OTC final monograph product. Several courts have rejected preemption arguments for OTC drugs after deciding that the CBE process is available for OTC label changes, but those decisions involved NDA products rather than monographs. *See Batoh v. McNeil-PPC*, *Inc*., 167 F. Supp. 3d 296, 317–18 (D. Conn. 2016); *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 698–702 (E.D. La. 2014); *Newman v. McNeil Consumer Healthcare*, No. 10–CV–01541, 2012 WL 39793, at *5–12 (N.D. Ill. Jan. 9, 2012). None of the cases speaks to the monograph preemption issue, and manufacturers raising preemption in the monograph context must be prepared to educate a court about the key distinctions between these regulatory pathways.

Despite the lack of case law on the subject, *Mensing*'s preemption framework and the monograph system's conformity requirements make for a strong preemption defense once a final monograph is in effect.

Are Label Deviations Permitted if the Applicable Monograph Is Not Yet Finalized?

The more challenging question is whether a viable preemption argument exists when the applicable monograph is not yet final. This is a particularly acute question because the FDA has often delayed issuing final monographs and has extended tentative final monographs (TFMs) for decades. *See Cutler*, 818 F.2d at 895–96. As with a final monograph, a manufacturer lacks the power to change the TFM itself, which is part of the FDA's formal rulemaking. *See* 21 C.F.R. §330.10(a)(7)(ii)–(v) (allowing submission of comments, new data, and information for FDA consideration and treating same as a petition to amend the monograph if received late in the process).

Less certain is whether a manufacturer can legally market a drug that differs from the applicable tentative final monograph. One possible interpretation of the monograph regulations is that the "applicable monograph" in 21 C.F.R. §330.1's conformity requirement includes TFMs, thus mandating conformity with the TFM in the absence of a final monograph. If that is the case, the conformity requirement and unavailability of the CBE mechanism to alter the label independently provide a strong preemption defense.

Even if a monograph does not qualify as the "applicable monograph" under the regulations until it is finalized, the regulatory scheme arguably operates to give it the same effect. A TFM is the FDA's formal, albeit not final, assessment of the "conditions under which a category of OTC drugs or specific OTC drugs are generally recognized as safe and effective [(GRASE)] and not misbranded." 21 C.F.R. §330.10(a)(7)(i). In other words, a TFM specifies the requirements to market, legally, a drug that has not undergone an individual approval. *Id*. Failure to comply with a TFM could render a product misbranded and illegal for sale, placing the product and its manufacturer at risk of regulatory action.

Further, the FDA has indicated that products marketed under a TFM should conform to it. The agency's regulations provide that marketing certain products "with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action." 21 C.F.R. §330.13(b)(2). The FDA has issued warning letters when labeling does not conform to a TFM, and it has explained that "[p]ending a final monograph, the agency does not object to the marketing of OTC drugs *that meet the formulation and labeling requirements described in the relevant TFM*" or that are otherwise eligible for the OTC drug-review program. Letter from Alonza E. Cruse, District Director, Los Angeles District Office, U.S. Food and Drug Admin. *et al*., to Dr. Colette Cozean, President/CEO, Innovative Biodefense Inc. (June 30, 2015) (emphasis added); Letter from LaTonya M. Mitchell, Denver District Director, Public Health Service, U.S. Food and Drug Admin., to Boyd Ronald Johnson, Chief Executive Officer, Quadex Pharmaceuticals, LLC (May 7, 2012) (includes FDA finding that product was misbranded because a warning on the label was misleading).

In addition, the policy rationale behind the monograph process is at odds with allowing unilateral changes to individual labels governed by a TFM. The purpose of the monograph procedure is to synthesize discussion and consensus among experts about key ingredients that are common to thousands of drugs. Allowing a company to implement label changes unilaterally while other products with the same ingredient are marketed without those changes would run counter to the basic purpose of the expert consensus and consistency underlying the monograph process.

Yet the FDA has also suggested that manufacturers may submit changes to the language being considered in a tentative final monograph. When review of OTC drugs on the market began in 1972, the FDA announced a policy of "forbearance from legal action" to allow manufacturers to bring their warnings and other safety information "into conformity with the current medical knowledge and experience" before a monograph becomes final. Over-The-Counter Drugs, 37 Fed. Reg. 7807-01, 7808 (Apr. 20, 1972); *see also* 21 C.F.R. §330.12(d)(1); FDA, *Compliance Policy Guide*, sec. 450.200 (Oct. 1, 1980). But the forbearance policy underscores the basic point that manufacturers risk running afoul of federal law by using a different label even when the associated monograph is not yet final; if it were otherwise, a forbearance policy would be unnecessary. It also demonstrates the critical role of agency discretion: a manufacturer may only market a product whose label diverges from the TFM if the FDA, in its discretion, allows it. If the FDA disagrees with the modification, it may determine that the drug is misbranded and impose penalties. *See, e.g.,* Letter from Mitchell, to Johnson, *supra* (threatening seizure and other legal action based on its finding that product was misbranded because a warning on the label was misleading).

A decision from multidistrict litigation involving Tylenol illustrates the narrow confines of TFM product labeling. *See In re*

Tylenol, 144 F. Supp. 3d at 699. The product first entered the market under an NDA, but on the date relevant to the plaintiff's claims, it was marketed as a monograph product. After recounting a complicated regulatory history involving FDA rulemaking, various proposals by the manufacturer, and FDA discussions about label changes, the court concluded that the manufacturer could have modified its label, despite the lack of a regulatory mechanism to do so, because the company had previously stated that it would revise the acetaminophen labeling for its TFM products when similarly modifying its NDA products' labeling. But the product at issue was a monograph product, and the court was silent on how a manufacturer's ability to revise labeling for an NDA OTC product could grant it the ability to do so for a monograph product. The court also incorrectly concluded separately that *Mensing* was limited to generic drugs—a holding that is particularly suspect in light of the Third Circuit's subsequent interpretation to the contrary. *In re Tylenol (Acetaminophen) Mktg., Sales Practices & Prods. Liab. Litig.*, No. 2:12-CV-7263, 2015 WL 7075949, at *21–22 (E.D. Pa. Nov. 13, 2015); *see also Sikkelee*, 822 F.3d at 703–704 (discussing *Mensing* framework in an aviation case).

Any ability the FDA may suggest that manufacturers have to make "voluntary adjustments" to their labels is significantly undercut by these mixed messages from the agency and the significant risks that a manufacturer faces if the FDA determines that its product is misbranded or being marketed illegally.

The *In re Tylenol* court also relied on an FDA statement in a letter that "[u]nder a TFM, manufacturers market products at their own risk and are able to make voluntary adjustments." *In re Tylenol*, 144 F. Supp. 3d at 730–31 (internal quotation marks omitted). But both the FDA and the court undercut the position that McNeil, the product manufacturer, was permitted to vary its label from the TFM—the FDA by repeatedly telling McNeil that the company must revise its dosing instructions to conform to the TFM, and the court by holding that the product was no longer considered safe and effective for marketing once it deviated from the TFM. *Id.* at 712 & n.71, 731 n.170 ("Extra Strength Tylenol could not be considered GRASE because the defendants were marketing it with dosing instructions that did not conform to the TFM."). Any ability the FDA may suggest that manufacturers have to make "voluntary adjustments" to their labels is significantly undercut by these mixed messages from the agency and the significant risks that a manufacturer faces if the FDA determines that its product is misbranded or being marketed illegally.

In re Tylenol is also instructive on the meaning of "conformity" with a tentative final monograph. From 1977 until 2011, the Extra Strength Tylenol dosing instructions allowed two tablets every 4 to 6 hours, while the TFM recommended two tablets every 6 hours. *Id.* at 711–12. When McNeil sought permission to add an alcohol warning, the FDA informed McNeil that its OTC label was not in "conformity" with the TFM's dosing instructions and requested that the label be revised. *Id.* McNeil later changed the dosing instructions to match the TFM. One of the plaintiff's liability theories was that the older label was in effect at the time of injury, and the court stated that the product was not in conformity with the TFM because of the difference in dosing instructions. This suggests that "conformity" requires strict adherence to the applicable TFM and that deviations must be very limited. That understanding supports a preemption defense by showing that manufacturers cannot independently provide meaningfully different warnings than those included in a product's TFM. *See Mensing*, 564 U.S. at 620 ("The question for "impossibility" is whether the private party could independently do under federal law what state law requires of it.").

Preemption of claims involving products governed by a TFM remains an open question. The issue was raised before the United States Supreme Court after *Mensing* was decided, but it did not reach the merits stage. Petition for Writ of Certiorari, *McNeil-PPC, Inc. v. Hutto*, No. 12-122, 2012 WL 3058321 (involving pediatric acetaminophen marketed through the monograph process), *cert. denied* 133 S. Ct. 428 (2012). Given the large number of products marketed under a TFM, and the ongoing progression of preemption jurisprudence stemming from *Mensing*, this area of the law will likely continue to develop.

An Alternative Basis for Preemption for Monograph and Other OTC Drugs

In addition to examining the monograph-specific restrictions, a manufacturer of any OTC product should consider another possible basis for preemption: 21 C.F.R. §201.66, also known as the Drug Facts Rule. The Drug Facts Rule contains standardized content and format requirements for all OTC drugs, whether marketed under a monograph, an NDA, or an ANDA. The OTC drug-labeling format, now ubiquitous and well recognized, includes the title, headings, subheadings, and location of any graphical images and bar lines. 21 C.F.R. §201.66(d). More importantly for preemption purposes, the regulations may also specify the content of the drug's warnings and other label information. *E.g.,* 21 C.F.R. §201.66(c). In fact, content requirements must be followed "unless otherwise specifically provided in the applicable monograph or regulation." 21 C.F.R. §201.66(a). The Drug Facts Rule recognizes that warnings required for a particular drug can be found in OTC drug regulations as well as that drug's monograph or approved drug application, as applicable, and incorporates those sources into the required label. 21 C.F.R. §201.66(c)(5)(viii).

The Drug Facts Rule cites specific warning language that must be included in OTC drug labels where applicable. *See* 21 C.F.R. §201.66(c)(1)–(8). It cross-references related labeling regulations containing spe-

cific content requirements, including such warnings as Reye's syndrome for salicylate products, and liver warnings and stomach bleeding warnings for analgesic or antipyretic drugs. 21 C.F.R. §201.66(c)(5)(ii). The Drug Facts Rule also mandates that a label "shall contain… [a]ny required warnings in an applicable OTC drug monograph, other OTC drug regulations, or approved drug application" not specifically listed in the rule. 21 C.F.R. §201.66(c)(5)(viii).

This mandatory language in the Drug Facts Rule appears to form the basis of a preemption defense under *Mensing*'s framework. The Drug Facts Rule does not provide a general mechanism akin to a CBE that would allow a manufacturer to deviate from the regulations' mandatory language, and drugs with a final monograph cannot undergo a label change without FDA action or permission. And most of the regulations cross-referenced by the Drug Facts Rule do not specify that a CBE may be available for label updates. When a cross-referenced regulation specifically adopts the CBE process, it appears limited to products marketed under an NDA or ANDA but not monograph products. *See, e.g.,* 21 C.F.R. §201.326(c) (providing that holders of "approved applications for OTC drugs" must submit supplements to include the "required information" under 314.70(c), the CBE regulation).

Further, section 201.326(c) states that "such labeling [the liver injury and stomach bleeding warnings] may be put into use without advance approval of FDA provided it includes at least the exact information included in paragraph (a) of this section." This provision could be interpreted to suggest that holders of approved applications can provide additional warning information beyond that which the rule specifies. But again, this subsection does not cover monograph products. An open question, however, does exist: could NDA application holders add language that materially alters the meaning and significance of the language specified in the rule? Perhaps, though another interpretation is that section 201.326(c) simply specifies the process to follow to update NDA products' labels with the newly added warnings in that regulation. How this provision applies is unclear.

An even more interesting implication of this section may be the unavailability of the CBE mechanism even for NDA products in most scenarios implicating the Drug Facts Rule and its cross-referenced regulations. Because some cross-referenced regulations contain a provision that explicitly adopt the CBE mechanism, while others, and the Drug Facts Rule itself, omit such a provision, one could argue that the CBE mechanism generally is not available for changes made in connection with the Drug Facts Rule regulations. Instead, under that interpretation, the CBE process would be available only if the applicable regulation specifically permits it. *See, e.g.*, 21 C.F.R. §201.326(c).

Section 201.326 has been discussed in only one case: *In re Tylenol*. *See* 144 F. Supp. 3d at 713–14, 726–28. There, the company implemented the warnings described in section 201.326(c), and as it explained to the court, the company could not alter those warnings or use the CBE process more generally for label changes to its monograph product. *Id.* at 727–29. The court, however, refused to apply *Mensing*'s framework and instead considered only the demanding "clear evidence" standard of *Wyeth v. Levine*. *Id.* It failed to recognize that the regulatory requirement to use specific language in the label is directly analogous to the requirement at issue in *Mensing*, in which the generic drug was required, by statute and regulation, to have the same labeling as its brand-name equivalent. *Mensing*, 564 U.S. at 612–13.

The conflict between the language mandated by federal regulation and the language that a plaintiff would require as part of a tort lawsuit is apparent. The decision in *In re Tylenol* notwithstanding, lawsuits attacking label language that is mandated by the Drug Facts Rule or the regulations that it cross-references present a direct and irreconcilable conflict between a manufacturer's state and federal duties.

Conclusion

The regulatory scheme that governs over-the-counter products is multifaceted and complex, but it can provide drug manufacturers with an important defense in product liability suits. The monograph process requires conformity to the FDA-developed monograph and does not provide a mechanism by which manufacturers may independently alter their product labels. And for monograph and NDA drugs alike, the Drug Facts Rule and the associated regulations impose specific labeling requirements for particular groups of drugs. These federal restrictions implicate the fundamental holding of *PLIVA, Inc. v. Mensing* and thus provide a viable preemption defense to product liability suits involving over-the-counter products. FD