No. _____

IN THE

Supreme Court of the United States

JOHNSON & JOHNSON AND MCNEIL-PPC, INC.,
Petitioners,

v.

LISA RECKIS AND RICHARD RECKIS,
Respondents.

On Petition for a Writ of Certiorari to the Supreme Judicial Court of Massachusetts

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In *Wyeth v. Levine*, this Court explained that state tort claims against drug manufacturers for failing to provide additional warnings would be preempted if "clear evidence" shows "that the FDA would not have approved a change to [the drug's] label." 555 U.S. 555, 571 (2009). The question presented is:

Whether the Massachusetts Supreme Judicial Court erred when it held, in direct conflict with the Seventh Circuit, that FDA's rejection of warning language proposed in a Citizen Petition is not "clear evidence" sufficient to preempt state tort claims that the manufacturer was obligated to add the FDA-rejected language to its drug's labeling.

PARTIES TO THE PROCEEDING

Petitioners, the Appellants below, are McNeil-PPC, Inc. ("McNeil") and its corporate parent Johnson & Johnson.

Respondents, the Appellees below, are Lisa Reckis and Richard Reckis, who sued both individually and as the parents and natural guardians of their minor child, Samantha Reckis.

RULE 29.6 DISCLOSURE

Johnson & Johnson is a corporation the securities of which are publicly traded. Johnson & Johnson does not have a parent corporation and there is no publicly held corporation that owns ten percent or more of its stock.

McNeil is a wholly owned subsidiary of Ortho-Clinical Diagnostics, Inc., which is a wholly owned subsidiary of Janssen Pharmaceuticals, Inc., which is a wholly owned subsidiary of Johnson & Johnson.

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The Supreme Judicial Court's ("SJC") opinion is reported at 28 N.E.3d 445 and reprinted in the Appendix ("App.") at 1a-46a. Its unpublished order denying Petitioners' Petition for Rehearing is reprinted at App. 47a-48a. The trial court's unpublished opinions denying Petitioners' Motions for a New Trial and for Judgment Notwithstanding the Verdict are reprinted at App. 56a-62a and 63a-67a, respectively. Its oral decision denying Petitioners' Motion for Summary Judgment is reproduced at App. 68a-70a.

JURISDICTION

The SJC issued its decision on April 17, 2015, and denied a timely petition for rehearing on June 10, 2015. App. 47a. On August 21, 2015 Justice Breyer granted Petitioner's motion to extend the date for filing this Petition to October 8, 2015. This Court has jurisdiction under 28 U.S.C. § 1257(a).

STATUTORY PROVISIONS INVOLVED

The pertinent constitutional, statutory, and regulatory provisions involved are reprinted at App. 194a-227a. The FDA decision addressing the Citizen Petition at issue in this litigation is reproduced (with its enclosures) at App. 146a-93a.

STATEMENT OF THE CASE

A. Introduction

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court established two rules governing whether the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C.

§ 301 *et seq.*, preempts state-law tort claims predicated on a pharmaceutical manufacturer's failure to provide additional product warnings. On one hand, the Court held that such state-law claims are *not* preempted if FDA would have allowed the manufacturer to alter its previously approved labeling unilaterally—that is, without FDA's prior approval. 555 U.S. at 568-70; *see also PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2581 & n.8 (2011). On the other hand, the Court recognized that such claims would be preempted where "clear evidence" shows "FDA would not have approved a change to [the drug's] label" because in that circumstance there would be a conflict between the state and federal labeling requirements. *Wyeth*, 555 U.S. at 571.

In the intervening years, the lower courts repeatedly have observed that *Wyeth* "[did] not define 'clear evidence,'" *In re Fosamax (Alendronate Sodium) Products Liab. Litig.*, 951 F. Supp. 2d 695, 703 (D.N.J. 2013), or even "suggest the level of proof required to constitute such evidence." *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1270 (W.D. Okla. 2011); *see also Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010) ("The Supreme Court ... did not clarify what constitutes 'clear evidence.'"); *Schilf v. Eli Lilly & Co.*, No. 07-4015, 2010 WL 3909909, at *4 (D.S.D. Sept. 30, 2010) ("After *Wyeth*, lower courts are left to determine what satisfies this 'clear evidence' standard in each case.").

Not surprisingly, the lack of a defined standard to guide this recurring inquiry has generated significant confusion among the lower courts. Though some courts have endeavored to apply the "clear evi-

dence" standard in a manner faithful to *Wyeth*, others have exploited the lack of clear guidance from this Court to let state-law claims proceed even where those claims directly contradict FDA's prior decisionmaking. This case, which squarely splits with the Seventh Circuit's decision regarding the same product, perfectly illustrates these competing approaches.

Respondents here asserted state tort claims premised on Petitioners' allegedly inadequate warnings, even though FDA expressly rejected the additional language Respondents claimed was necessary. Faced with the same allegations targeting the precise drug warnings at issue here, the Seventh Circuit held that FDA's prior rejection of a so-called Citizen Petition proposing additional warnings constituted the "clear evidence" *Wyeth* said was needed to preempt such claims. *See Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861 (7th Cir. 2010) (Posner, J.). In stark contrast, the Massachusetts Supreme Judicial Court ("SJC") looked at the same record and reached the opposite result: It affirmed one of the largest verdicts in Massachusetts history—approximately $140 million including interest.

In breaking from the Seventh Circuit's approach, the SJC (like other courts resistant to federal preemption) erected hurdles so high that it is hard to imagine any case satisfying the "clear evidence" standard it articulated. In the SJC's view, FDA's unqualified rejection of a proposed warning including the very language plaintiffs later propose is not enough unless FDA also explains that it would separately reject each individual part of the proposed

warning. Moreover, the SJC's decision establishes a *per se* rule that FDA's prior rejection of a proposed warning is legally irrelevant unless the language was proposed by the drug's manufacturer—an astonishing position premised on the SJC's apparent belief that FDA's decisionmaking hinges on the identity of the party that proposed new warning language rather than the proposal's scientific merits.

Neither rule has any basis in *Wyeth* or common sense. *Wyeth* did not articulate a preemption rule only to invite parties to evade it by superficially modifying the language already rejected by FDA. And nothing in *Wyeth* made federal preemption contingent on the identity of the party who proposed the warnings FDA rejected. Instead, the Court's standard turned on clear evidence of *FDA's position about the warning*, and thus accords the Agency's regulatory decisionmaking the respect it deserves.

The SJC's twin holdings directly conflict with that approach. They trivialize FDA's careful process for evaluating product labeling by assuming that FDA's evaluation of proposed warnings is tied inflexibly to the exact words advocated. Even worse, they assume that FDA's decisionmaking is dictated by the source of proposed labeling changes rather than the Agency's informed determination of their merit. And while the SJC's analysis would be problematic in any context, it is especially troublesome when it comes to over-the-counter (OTC) drugs like the Children's Motrin® product at issue in this litigation. Because OTC labels are intended for consumers rather than trained medical professionals, FDA aims not only to communicate risk information but to avoid scaring

consumers away from beneficial treatments. FDA applied that principle when it rejected the language Respondents later advocated at trial, and the SJC's decision thereby directly undermines the statutory and regulatory objectives that underpin FDA's decisionmaking in this context.

The SJC's decision also conflicts with other aspects of this Court's preemption jurisprudence. Taken literally, the decision would subject manufacturers to state-law liability unless they attempt labeling changes *that FDA has already rejected*, even (as here) when there is no new data that might warrant revisiting the Agency's prior determinations. That approach directly conflicts with the recognition by other courts that federal law allows manufacturers to initiate labeling changes only to "reflect newly acquired information." *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 37 (1st Cir. 2015) (internal quotation omitted). And in contravention of this Court's instructions, the SJC's approach would force manufacturers "to submit a deluge" of duplicative requests and thereby impose undue "additional burdens" on FDA. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001).

Particularly given the record here, this case is an ideal vehicle for providing much-needed guidance to the lower courts and restoring content to the "clear evidence" standard. It is *undisputed* that FDA expressly considered and rejected the very language on which Respondents' claims were based. And unlike *Wyeth*, where there was "no evidence" that FDA "gave more than passing attention" to the issue, 555 U.S. at 572 (quoting the trial court's factual find-

ings), it is undisputed that FDA evaluated the current scientific literature and available risk information from all product manufacturers and then made nuanced decisions about how best to address the risks of SJS/TEN—namely, by deciding *not* to add the very words later proposed by Respondents. Yet the state court nonetheless upheld a historic damages award predicated entirely on Petitioners' failure to include the language FDA rejected.

The Petition should be granted and the SJC's decision reversed.

B. Regulatory and Factual Background

This case involves Respondents' claim that the FDA-approved warnings for Petitioners' OTC Children's Motrin® were inadequate because they did not contain language that allegedly would have caused Plaintiff-Respondent Richard Reckis to forgo giving the drug to his daughter Samantha. The suit claims that as a result of Petitioners' inadequate labeling, Samantha contracted Toxic Epidermal Necrolysis (TEN), a rare skin disorder that begins with rash-like symptoms and can (as here) progress to life-threatening burn-like blistering of the skin.

A Massachusetts jury agreed and awarded Respondents $63 million in compensatory damages—the single largest award ever in a Massachusetts individual personal injury action. With accumulated prejudgment statutory interest at 10% per year, the total judgment now exceeds $140 million.

Throughout the case, Petitioners asserted that federal law preempted Respondents' claims because

FDA rejected the warning language Respondents later claimed was necessary. Nonetheless, the courts below denied Petitioners' federal preemption defense.

1. Federal Regulation of OTC Product Labeling

The FDCA charges FDA with determining whether a given drug is safe and effective "under the conditions prescribed, recommended, or suggested in [its] proposed labeling." 21 U.S.C. § 355(d). FDA must therefore weigh the risks associated with each drug against its therapeutic benefits and strike a balance between these often-competing considerations by regulating the content of the drug's labeling. 21 C.F.R. § 314.50(d)(5)(viii) (requiring each new drug application to include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling").

In this way, "[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective." FDA, *New Drug and Antibiotic Regulations*, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). Therefore "[t]he centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006).

Unlike prescription-drug labeling, OTC labels are intended for the general public rather than medical professionals. As a result, FDA must ensure that OTC product labeling is communicated in a way that allows laypeople to make appropriate product-use decisions without physician guidance. *See id*. at 3931. FDA therefore has adopted strict requirements for OTC labels, 21 C.F.R. § 201.66, and has explained that its regulations aim not only to convey risk information but to do so in a way that does not "appear[] overwhelming" or "present[] a 'cognitive load'" that could induce poor product-use decisions (including abstention from otherwise-beneficial product use). *See* FDA, *Over-The-Counter Human Drugs—Labeling Requirements*, 64 Fed. Reg. 13254, 13255 (Mar. 17, 1999).

2. The Citizen Petition Process

Once FDA approves OTC product labeling, there are at least three avenues for changing it. First, FDA may initiate its own labeling review for a drug or class of drugs and then issue revised labeling templates (as it did here, *see infra*). Second, where manufacturers believe that new risk information or analysis warrants revisions to comply with federal labeling requirements, FDA permits them to revise their labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" without prior FDA approval. 21 C.F.R. § 314.70(c)(6)(iii). As *Wyeth* explained:

> Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application. There is, however, an FDA regulation that permits a manufac-

> turer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" (CBE) regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

555 U.S. at 568 (quoting 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C)). NDA holders must submit CBE supplements to FDA for ultimate approval, 21 C.F.R. § 314.70(c)(6), and FDA has plenary authority to accept, modify, or reject CBE changes. *Id.* § 314.70(c)(7).

Third, FDA allows any person to petition the Agency "to issue, amend or revoke a regulation" or "take or refrain from taking any other form of administrative action." *Id.* § 10.25(a). FDA must address each such "Citizen Petition" on the merits. *Id.* § 10.30(e)(1); *see also* Carrier & Wander, *Citizen Petitions: An Empirical Study*, 34 Cardozo L. Rev. 249, 262 (2012) ("[T]he agency is required to address the merits of every citizen petition submitted."). In doing so, it "may grant or deny such a petition, in whole or in part, and may grant such other relief or take other action as the petition warrants." 21 C.F.R. § 10.30(e)(3); *see also* Carrier & Wander, *supra*, at 266 ("The FDA sometimes issues 'mixed' de-

cisions, which grant in part and deny in part the petition.").

For each Petition, FDA creates a public docket and invites public comment. 21 C.F.R. § 10.30(d). FDA then thoroughly reviews the issues raised, using resources across the Agency. "The data and information submitted with these petitions require detailed analysis and precise scientific documentation, often involving multiple disciplines within [FDA]." *The Generic Drug Maze: Speeding Access to Affordable, Life-Saving Drugs—Hearing Before the S. Spec. Comm. on Aging,* 109th Cong. 14 (2006) (statement of Gary Buehler, Director, FDA Office of Generic Drugs). FDA also conducts a "thorough legal review" of the Petition, *id.*, and ultimately issues an official written response. 21 C.F.R. § 10.30(e)(2).

3. Children's Motrin® and TEN

Children's Motrin® is a brand-name version of OTC ibuprofen, one of the most widely used and effective pain and fever medicines. FDA first approved ibuprofen as safe and effective for adult prescription use in 1974; adult OTC use in 1986; pediatric prescription use in 1989; and pediatric OTC use in 1995. The medicine remains available in both prescription and OTC formulations and is sold by multiple manufacturers under various brand names (*e.g.*, Advil®, Motrin®, Nuprin®) and as a generic. FDA estimates that U.S. pharmacists dispense more than 29 million ibuprofen prescriptions and more than 100 million people take OTC ibuprofen every year. App. 153a-54a.

Over the years, researchers have suggested a

connection between ibuprofen and TEN as well as its less severe variant, Stevens Johnson Syndrome (SJS, collectively SJS/TEN). App. 150a & n.3. These immune-mediated diseases attack the skin and mucous membranes and are idiosyncratic—meaning it is impossible to predict in advance who is at risk. App. 155a. Fortunately, both SJS and TEN are extraordinarily rare. FDA estimates that there are only 1.2-to-6 SJS cases and 0.4-to-1.2 TEN cases per-million persons per-year from all causes combined. App. 154a.

The medical literature continues to debate whether ibuprofen can cause SJS or TEN. For some other drugs, the demonstrated association with SJS/TEN is strong enough that FDA classifies them as "highly suspected," but ibuprofen is not in that class. And because SJS/TEN typically starts with fever or malaise—the very conditions ibuprofen treats—*before* rash or blisters develop, attributing causation to ibuprofen is challenging. *See Robinson*, 615 F.3d at 868 (describing the "difficult[y]" in "determining the direction of causation"). Two large epidemiologic studies have investigated the degree of association between ibuprofen and SJS/TEN; the first found a statistically significant association, but the most recent and comprehensive study (published by the same lead investigator as the earlier study), found no statistically significant association. *See* Mockenhaupt et al., *Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis: Assessment of Medication Risks with Emphasis on Recently Marketed Drugs: The EuroSCAR Study*, 128 J. INVESTIGATIVE DERMATOLOGY 25 (2008).

4. OTC Motrin® Labeling in 2003

When FDA first approved ibuprofen for OTC pediatric use in 1995, it was well-aware of reports that ibuprofen was associated with SJS/TEN, and it considered those reports as evidence that ibuprofen could cause SJS/TEN. In fact, the FDA-approved prescription label for ibuprofen—directed to medical professionals—had long noted the existence of such reports and suggested a causal relationship. *See, e.g.*, App. 124a-28a.

Nevertheless, FDA decided not to include a similar reference on the OTC ibuprofen labeling, including for Children's Motrin®. The reason is simple: Prescription labels are intended for doctors and are therefore far more extensive and detailed than OTC labels. OTC labels, by contrast, are intended for consumers; instead of detailing every potential rare adverse reaction, OTC labels provide directions for safe use and instruct consumers what to do if an adverse reaction occurs.

As the Seventh Circuit explained in *Robinson*, when FDA allows a drug to be sold OTC, it does so based on a regulatory determination that the drug is safe and effective for use without physician supervision, notwithstanding possibly serious adverse reactions in rare cases. 615 F.3d at 869-70. When determining appropriate OTC labeling, FDA thus seeks to craft warnings that (1) ensure consumers know when to seek medical help but (2) avoid deterring consumers from beneficial product use by placing undue emphasis on remote risks. *See Dowhal v. SmithKline Beecham Consumer Health-Care*, 88 P.3d 1, 14 (Cal. 2004) ("The mere existence of the

risk ... is not necessarily enough to justify a warning; the risk of harm may be so remote that it is outweighed by the greater risk that a warning will scare consumers into foregoing use of a product that in most cases will be to their benefit."). In addition, FDA must ensure that OTC labels are not so laden with detail about remote risks that they become useless. *Robinson*, 615 F.3d at 869-70 ("The resulting information overload would make label warnings worthless to consumers."); *see also* 21 C.F.R. § 330.10(a)(4)(v) (OTC labels should be written so "as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use").

Pursuant to this mandate, FDA has always exercised close control over Petitioners' OTC Children's Motrin® label. In 1998, it issued class labeling for all OTC ibuprofen products, rejecting individual labeling changes proposed by McNeil. In 1999, FDA issued comprehensive new labeling regulations for all OTC medicines, establishing the now-familiar "Drug Facts" format designed to standardize labeling categories. FDA itself drafted the new OTC ibuprofen labeling required to satisfy these regulations. That labeling, approved in October 2000, ordered that the following relevant warnings and instructions be included:

> ***WARNINGS***:
>
> **Allergy Alert:** Ibuprofen may cause a severe allergic reaction which may include:
>
> ▪ hives ▪ facial swelling

▪ asthma (wheezing) ▪ shock

* * *

Do not use if the child has ever had an allergic reaction to any other pain reliever/fever reducer.

* * *

Stop use and ask a doctor if ...

- an allergic reaction occurs. Seek medical help right away.
- pain or fever gets worse or lasts more than 3 days
- the child does not get any relief within first day (24 hours) of treatment
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

Trial Exh. 44 (SJC App. Vol. 24—Page 11498, quoted in part at App. 10a).

All ibuprofen manufacturers used this same FDA-approved template; none provided more detailed warnings about SJS/TEN.

5. 2005-2006 Labeling Review

In early 2005, FDA announced new recommendations arising from its comprehensive review of the risks and benefits of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen. App. 71a-110a

(the "April 2005 memorandum). Though that review largely was focused on potential cardiovascular risks associated with NSAIDs, the Agency's April 2005 memorandum noted that at least one prescription NSAID already contained a boxed warning for SJS/TEN and that FDA had a received a February 2005 Citizen Petition (co-authored by one of Respondents' eventual expert witnesses in this case) "regarding the risk of [SJS] with ibuprofen." App. 96a & n.8.

That Petition had asserted that the then-approved prescription and OTC ibuprofen labeling did not adequately warn about SJS/TEN, and (among other things) requested that FDA either withdraw approval for OTC ibuprofen or require that its labeling warn explicitly that rash or blisters could progress to "life-threatening" diseases or reactions including SJS/TEN. App. 142a.[1] FDA's April 2005

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[1] In particular, the Petition requested the following labeling changes:

- In the "***Warnings***" section: **"Serious Skin Reactions:** Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate attention if any of these symptoms develop while taking ibuprofen."

- In the "***Stop use and ask a doctor if***" section: "a skin rash or blisters on the eyes, mouth or

memorandum explained that the Petition remained under review, but that "based on analyses of data obtained before the petition was submitted, the agency has determined that the labeling for non-prescription NSAIDs should be updated to warn of the potential for skin reactions," and announced that it would make a final decision on whether any further labeling changes were warranted after completing its review of the Petition. App. 96a n.8.

Following the April 2005 memorandum, but before it responded to the Citizen Petition, FDA issued revised labeling templates for both prescription and OTC ibuprofen products, which remain in effect today. For *prescription ibuprofen labeling directed to physicians*, FDA supplemented the existing references to rare adverse event reports of SJS/TEN with a statement in the "Warnings" section that "NSAIDs ... can cause serious skin adverse events such as ... Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal." App. 159a. FDA also issued a "Medication Guide" for patients taking *prescription ibuprofen under a physician's direction*, which included a statement that skin reddening, rash, or blisters could be early signs of "life-threatening skin reactions." App. 160a.

In notable contrast, however, FDA did not in-

> genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis."

App. 142a-43a.

clude explicit references to SJS, TEN, or "life-threatening skin reactions" in the revised OTC labeling for ibuprofen products, including Children's Motrin®. App. 162a. Instead, it added three potential early symptoms of such a reaction—"skin reddening," "rash," and "blisters"—to the label's "Allergy Alert" section instructing consumers to stop using the medicine and seek medical help if those symptoms occurred. *Id*.

In June 2006, FDA issued a comprehensive response to the Citizen Petition. The Agency began by noting that it had analyzed all available safety data on ibuprofen, including a search of its Adverse Event Reporting System (AERS) "for domestic reports of SJS/TEN with all ibuprofen products (prescription and OTC) during its marketing history from 1975 through March 2005." App. 152a.[2] As a result, FDA's review examined reports not only concerning Children's Motrin®, but for *all* ibuprofen products.

Based on that review, FDA agreed with the Petition that ibuprofen can cause SJS/TEN in rare cases, but it declined to remove OTC ibuprofen from the market. Instead, it explained that the Citizen Petition greatly overstated the incidence of SJS/TEN, App. 150a, and observed that alternative "OTC drugs for short-term relief of pain and fever can also be associated with serious, potentially life-threatening adverse events." App. 163a. It therefore

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[2] The FDA Adverse Effect Reporting System contains all reports of adverse reactions that must be reported by manufacturers, along with reports that healthcare professionals and consumers submit. *See* 21 C.F.R. 314.80.

concluded "that the overall benefit versus risk profile for ibuprofen products remains very favorable when they are used according the [then-current] labeling instructions" and that continued OTC access to ibuprofen remained "in the interest of the public health." App. 163a.

With specific reference to the Petition's proposed OTC labeling changes, FDA explained that it already had supplemented the "Allergy Alert" template to highlight potential "skin reddening," "rash," and "blisters," and that consumers would be warned to "stop use and seek medical help right away" if those symptoms developed. App. 162a. It therefore "granted" the relief requested in the Petition to that extent. App. 164a.

Beyond those changes, however, FDA's decision definitively rejected the Petition's request for additional OTC ibuprofen warnings—including the requests to warn that rash or blisters could progress to "life-threatening diseases" or reference SJS/TEN by name—explaining that "a description of symptoms" with instructions to seek medical help "more appropriate[ly]" communicated the relevant risk information to the OTC target audience (*i.e.*, ordinary consumers). App. 162a. It added that:

> We do not believe that it is useful to include the specific terms *SJS*, *TEN*, or *erythema multiforme*, *Stevens-Johnson syndrome*, and *toxic epidermal necrolysis* in the OTC label because most consumers are unfamiliar with these terms. In addition, effective OTC labeling communicates warning information in a manner that consumers can quickly and easily

identify and understand.

Id. (italics in original).

Finally, FDA rejected a request to translate and disseminate foreign ibuprofen labeling—some of which references "life-threatening side effects." App. 163a; *see also* App. 136a. Instead, FDA reiterated that its previously "revised labeling templates for both OTC and prescription ibuprofen products most appropriately communicate the risks and benefits associated with their use." App. 163a. As they must, all OTC NSAID manufacturers continue to use FDA's 2005 labeling template today.

C. Richard Reckis's Administration of Children's Motrin® to his Daughter.

Respondents Richard and Lisa Reckis allege that inadequacy in the labeling of Children's Motrin® caused their daughter Samantha to contract TEN. Specifically, they assert that her disease and ensuing injuries would not have occurred if the Children's Motrin® label warned that a rash could be the start of "Toxic Epidermal Necrolysis" or, if not identified by name, a "life-threatening disease." App. 3a.[3] With that warning, they claim Richard would not have given Samantha a third dose of Children's Motrin® when her rash-like symptoms first appeared after taking a second dose. *Id.*

Respondents sued McNeil and Johnson & John-

[3] The labeling already included instructions to stop use and seek medical help if an "allergic reaction" or "any new symptoms" appeared, App. 10a, but Mr. Reckis gave a third dose despite noticing the rash. App. 3a.

son in Plymouth Superior Court in January 2007. The case went to trial in January 2013 on a theory of negligent failure to warn. Respondents introduced expert testimony that discontinuing the medicine after the second dose would have avoided Samantha's injuries. Mr. Reckis also testified that he would not have administered a third dose if the labeling had warned that his daughter's rash "could be the warning sign of [TEN] or [SJS]," and that he likewise would not administered the final dose if the labeling warned that such a rash "might be the pathway to a life-threatening disease." App. 16a n.3. The jury returned a verdict in Respondents' favor and awarded a record $63 million in compensatory damages. App. 49a-52a.

McNeil and Johnson & Johnson had filed timely motions for summary judgment, directed verdict, and judgment notwithstanding the verdict, each asserting that Respondents' claims were preempted. The trial court denied all three motions, along with a motion to remit the damages award. App. 56a-70a. Petitioners sought direct review in the SJC, advancing the same federal preemption argument. The court accepted the direct appeal, but rejected Petitioners' preemption argument and declined to overturn the damage award. App. 1a-46a.

With respect to preemption, the SJC first acknowledged that Respondents' claim would be preempted if the jury predicated its verdict on Petitioners' failure to give warnings that FDA would not have allowed. It therefore conceded that federal preemption principles barred any claim that "the Children's Motrin label should have mentioned SJS

and TEN by name" because FDA rejected the addition of such warnings when it answered the Citizen Petition. App. 20a.

The SJC acknowledged that its holding on this point ordinarily would have required a new trial under state law. App. 26a-27a. But the SJC pronounced itself "reasonably confident" that the jury did not base its determination on that clearly preempted theory because, among other things, Mr. Reckis had testified that he would not have recognized the medical terms SJS or TEN and because Respondents' counsel did not press in closing argument the contention that the labeling should have included those terms. App. 27a-28a. According to the SJC, the jury therefore must have based its verdict on Respondents' alternate theory that the OTC labeling should have warned that a rash could lead to a "life-threatening disease," rather than on Petitioners' failure to reference SJS and TEN by name.

Yet as Petitioners repeatedly explained, that language—just like the references to SJS and TEN by name—likewise had been proposed in the Petition and rejected by FDA in its response. Even so, the SJC held that FDA's rejection of this language did not supply the "clear evidence" needed to establish preemption under *Wyeth*. The court offered two rationales for this conclusion.

First, the SJC asserted that although the rejected Citizen Petition had indeed proposed a reference to "life-threatening disease," the Petition *also* had requested that the labeling use the disease names. App. 23a. That was critical, according to the court, because FDA's Citizen Petition response did not ex-

pressly state that it would have reached the same conclusion if the Petition had sought *only* a reference to "life-threatening diseases" without also mentioning specific disease names. In the SJC's view, that made it "anybody's guess" whether FDA would have rejected a stand-alone proposal to reference "life-threatening diseases." *Id.* at 23a-24a.

Yet the court made no effort to square that conclusion with the law or the facts. It never acknowledged that FDA's regulations expressly authorize the Agency to approve Petitions "in whole or in part, and [to] grant such other relief or take other action as the petition warrants." 21 C.F.R. § 10.30(e)(3). Nor did it grapple with the fact that FDA exercised precisely that authority here—before affirming that its final labeling decision (including its omission of language warning of "life-threatening disease") represented the "most appropriate[]" means of communicating the pertinent risks and benefits. App. 163a.

Second, despite FDA's legal obligation to address every Citizen Petition based on its scientific merits, the SJC speculated that FDA might have issued a different decision had the request come from Petitioners. App. 24a ("[E]ven assuming … FDA would have rejected a citizen petition to add only this warning [regarding 'life-threatening disease'], that would not answer whether the FDA would have rejected the warning had it been sought by defendants themselves."). In other words, the court seemingly adopted the view that FDA makes life-and-death decisions based on the identity of the petitioner—not on whether a given request is consistent with the

scientific data, pertinent legal requirements, and the Agency's obligation to promote the public's health.

Once again, the SJC offered no colorable basis for that conclusion—much less for thinking FDA acted that way here. The court did not even speculate (much less give a reason to believe) that Petitioners (or any other manufacturer) had relevant information or analysis not available to FDA when it answered the Citizen Petition. On the contrary, FDA's response shows that it comprehensively reviewed the available literature and pertinent adverse events reported to FDA over a 30-year period—including reports made to *all* manufacturers. That is far more data than Petitioners alone could have offered. Instead, the SJC simply asserted that FDA is *generally* overburdened and that manufacturers *sometimes* have superior access to emerging risk information, App. 25a n.30, even though it could not identify any undisclosed risk information here, and even though FDA's calibrated response to the Citizen Petition—accepting some requests and rejecting others—demonstrated that FDA paid far more than "passing attention" to this issue. *Wyeth*, 555 U.S. at 572 (quotation omitted).

REASONS FOR GRANTING THE PETITION

I. THE LOWER COURTS ARE SPLIT OVER THE PROPER INTERPRETATION OF *WYETH*'S "CLEAR EVIDENCE" STANDARD.

Like this case, *Wyeth* arose from state-law claims that a drug manufacturer failed to provide adequate warnings. 555 U.S. at 559-60. In analyzing the de-

fendant's preemption claim, this Court made clear that the central question is whether FDA would have allowed the manufacturer to issue additional warnings without prior FDA approval. If so, the state-law claim can proceed: There would be no clear conflict between federal law and state law. But if not, *Wyeth* made clear that any such claim would be preempted because it would be impossible for the manufacturer to satisfy both its federal obligations (to use FDA's approved labeling) and state duties (to use different labeling). As a result, the question whether FDA would have approved a unilateral labeling change lies at the core of any preemption analysis in this context, and this Court has not hesitated to police that line in a series of post-*Wyeth* decisions finding preemption where the FDCA would have barred pharmaceutical manufacturers from using unapproved labeling. *See Mutual Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466 (2013); *Mensing*, 131 S. Ct. at 2567.

Consistent with this framework, *Wyeth* recognized that "FDA retains authority to reject" any new warning that a drug manufacturer seeks to implement. 555 U.S. at 571. It therefore held that state-law claims are preempted whenever there is "clear evidence that the FDA would not have approved a change," because in those circumstances it would be "impossible for [the manufacturer] to comply with both federal and state requirements." *Id.*

In *Wyeth*, however, no such "clear evidence" existed: "FDA had not made an affirmative decision to … prohibit Wyeth from strengthening its warning," and Wyeth did not contend that FDA had considered

the plaintiff's proposed labeling change in light of an updated risk-benefit analysis. *Id*. at 571-73. Instead, the Court found that FDA at best gave "passing attention" to the issue. *Id*. at 572 (quotation omitted). Accordingly, it declined to credit Wyeth's argument that FDA would have rejected the plaintiff's proposed change. *Id*. at 573.

As a result, the *Wyeth* Court had no opportunity to elucidate what satisfies the "clear evidence" standard. And in the absence of clear guidance from this Court, the lower courts have developed conflicting approaches on how to resolve this oft-recurring preemption issue. This case illustrates that conflict in spades.

Five years ago, the Seventh Circuit considered virtually identical state-law claims alleging that Petitioners' Children's Motrin® warnings were inadequate but held such claims preempted based on the same record evidence at issue here—FDA's rejection of the Citizen Petition invoked by Petitioners throughout this litigation. *Robinson*, 615 F.3d at 870, 873. In direct contrast, the SJC strained to affirm the massive damages award in this case despite FDA's decision—joining other courts that have turned *Wyeth*'s "clear evidence" standard into an all-but-insurmountable hurdle that eviscerates the legitimate preemptive force of FDA's decisionmaking and impedes the Agency's ability to fulfill its mission.

Though the SJC conceded that FDA comprehensively reviewed the relevant labeling and rejected requests to add the very words Respondents later advocated at trial, it bent over backwards to deny

Petitioners' preemption defense—holding in essence that minor changes in a given proposal can evade the preemptive force of FDA's decisionmaking, and that even FDA's unqualified rejection of the precise language proposed at trial carries no force unless it was proposed to FDA by the product's manufacturer.

As set forth below, neither approach to the "clear evidence" standard comports with *Wyeth* or common sense, and both impugn the integrity of FDA's decisionmaking. The key point here, however, is that those rigid tests for preemption split directly with *Robinson*, which had no trouble accepting the same evidence—FDA's response to the Citizen Petition—as sufficient to establish "clear evidence" that FDA would not have approved stronger OTC warnings about SJS/TEN that "recited its horrific consequences." *Id.* at 869; *see also id.* at 870, 873. This Court should resolve the split and end the evasions used by the SJC and other courts to convert *Wyeth*'s "clear evidence" standard into a virtual *per se* bar against federal preemption in this context.

A. The SJC's Decision Makes It Virtually Impossible To Satisfy *Wyeth*'s "Clear Evidence" Standard.

Though the SJC conceded that FDA rejected the precise language Respondents later proposed—that the words "life threatening" be added to the labeling—it hypothesized that FDA might have approved those words if only the Citizen Petition had not *also* sought specific mention of SJS/TEN. According to the SJC, it was "anybody's guess" whether "FDA also would consider including a mention of life-

threatening diseases, by itself, to be inappropriate" absent the additional request. App. 23a.

The import of that approach is clear: Under the SJC's ruling, FDA's explicit rejection of proposed labeling language is not preemptive unless the Agency also specifies that it would reject every variation or subset of the proposed language. But this Court did not articulate a "clear evidence" standard in *Wyeth* only to give plaintiffs a foolproof route to avoid it.

In any event, the SJC's assertions hinge on a demonstrably false premise. There is no all-or-nothing rule that forces FDA to reject language it might have deemed necessary simply because it was accompanied by further requests FDA deems unnecessary. Instead, FDA is expressly authorized to "grant or deny … a petition, in whole or in part, and [to] grant such other relief or take other action as the petition warrants." 21 C.F.R. § 10.30(e)(3). That is why FDA routinely "issues 'mixed' decisions, which grant in part and deny in part the petition," Carrier & Wander, *supra*, at 266, just like it did here. In addressing the Petition's requests for additional warnings, FDA granted the request for OTC labeling revisions to identify "skin reddening," "rash," and "blisters" as potential symptoms of serious allergic reactions, but denied the request for additional language that would have unduly emphasized such rare reactions, potentially deterring lay consumers from beneficial use of the drug. App. 161a-62a. Likewise, for the prescription labeling, the FDA granted a request to include a detailed warning about the potential risk of SJS and TEN, but denied a request to place it in a bolded black-box. App. 159a-60a.

Accordingly, the SJC's decision is inconsistent with federal law and refuted by the Agency's own actions in this case. The Agency has plenary authority to choose among a Petition's proposals (and indeed to craft alternate language), but rejected the language Respondents proposed here because it viewed those alarmist warnings as counterproductive in the OTC context (as opposed to the prescription-drug context).

Perhaps because the SJC's assertions on this point were so fanciful, the court sought to bolster its analysis by asserting (like certain other courts) that FDA might have reached a different decision if only Petitioners themselves had proposed these changes—rather than Respondents' own expert witness, who co-authored the relevant Petition. App. 24a (holding that FDA's decision does "not answer whether the FDA would have rejected the warning had it been sought by the defendants themselves"); *see also Schedin v. Ortho-McNeil-Janssen Pharm., Inc.*, 808 F. Supp. 2d 1125, 1133 (D. Minn. 2011) ("That the FDA did not require a label change, after it received the statutory authority to do so, in the face of a Citizen's Petition … not supported by the manufacturer[,] does not constitute clear evidence that the FDA would have rejected a label change proposed by Ortho-McNeil."), *aff'd in part, rev'd in part on other grounds* 700 F.3d 1161 (8th Cir. 2012); *Baumgardner v. Wyeth Pharm.*, 2010 WL 3431671, at *1 (E.D. Pa. Aug. 31, 2010) ("None of this evidence [involving FDA's rejection of Citizen Petitions] proves that the FDA would have rejected relevant warnings had Wyeth, the manufacturer, proposed them.").

That argument is even more problematic than the first. It has no basis in *Wyeth*, which easily could have announced (but did not announce) a *per se* rule conditioning federal preemption on the manufacturer-defendant having proposed a labeling change and FDA having rejected the manufacturer's request. FDA has an array of tools to regulate drug labeling (including self-initiated reviews and Citizen Petition decisions, both of which occurred here), and there is no conceivable reason why informed Agency decisions issued through those mechanisms cannot satisfy *Wyeth*'s "clear evidence" standard—especially when the SJC did not even suggest that Petitioners had late-breaking information that the Agency did not consider. Instead, the SJC's decision is simply an attack on FDA: It depends on the proposition that the Agency's decisions hinge on the proposing party's identity rather than the proposal's scientific merits.

That explains why the Seventh Circuit took a different approach, holding that FDA's denial of this Citizen Petition constituted "clear evidence" that FDA would have rejected the sort of labeling change at issue here. *See Robinson*, 615 F.3d at 873. And it is why other courts likewise have accepted FDA's response to a Citizen Petition as "clear evidence" without respect to the proposing party's identity. *See, e.g.*, *Dobbs*, 797 F. Supp. 2d at 1274 (finding "clear evidence" because "FDA rejected citizen petitions asking it to strengthen the suicidality warnings for Prozac"); *Dowhal*, 88 P.3d at 11 (holding that FDA's response to a Citizen Petition "established a federal policy prohibiting defendants from giving consumers any warning other than the one approved by the

FDA").

In contrast to these courts, the SJC simply refused to credit FDA's position—instead obligating Petitioners to disprove pure speculation that FDA would have changed its position if a different party had asked for the same warning, based on the same evidence already before the Agency. That approach has no basis in this Court's jurisprudence. *See Mensing*, 131 S. Ct. at 2580 (plurality opinion) ("[P]re-emption analysis should not involve speculation about ways in which federal agency and third-party actions could potentially reconcile federal duties with conflicting state duties.").

B. The SJC's Approach Exemplifies A Broader Tension Among The Lower Courts Over This Court's Preemption Jurisprudence.

As set forth above, the SJC's interpretation of *Wyeth*'s "clear evidence" standard effectively conditions federal preemption on the defendant having personally requested and FDA having rejected the precise warnings (and only the precise warnings) later proposed by a plaintiff. While that approach is impossible to square with this Court's cases, the SJC is hardly alone in crafting novel hurdles that undermine this Court's jurisprudence.

In *Mensing*, this Court rejected the argument that preemption does not apply where a defendant could have "asked the FDA for help" in effectuating a label change and instead instructed courts to focus solely on "whether the private party could independently do under federal law what state law re-

quires." 131 S. Ct. at 2579. Yet some courts nonetheless insist that manufacturers challenge or even violate the law to avoid liability. For example, in *Aaron v. Wyeth*, No. 2:07-CV-927, 2010 WL 653984 (W.D. Pa. Feb. 19, 2010), the court held that even though FDA "repeatedly rejected" proposed labeling changes, there was not "clear evidence" because the manufacturer "did not press its position" but "instead acquiesced to [FDA's] requests." *Id.* at *6. At least two other courts likewise have refused to find "clear evidence" even where FDA directed manufacturers not to issue additional warnings, on the theory that the manufacturers could have found an alternative, off-label means of communicating the plaintiffs' proposed warnings. *Schilf*, 2010 WL 3909909, at *4 (rejecting preemption defense because manufacturer had not proven that FDA would have rejected attempts "to 'get the word out' in other ways [besides labeling]"); *Wells v. Allergan, Inc.*, No. 12-973, 2013 WL 389147, at *7 (W.D. Okla. Jan. 31, 2013) (rejecting preemption defense because the defendant allegedly could have communicated the FDA-rejected warnings via email or during informal visits to doctors' offices).

Other courts effectively require manufacturers to prove that FDA would have taken enforcement action against them for making an unapproved label change. In *Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948 (E.D. Wis. 2009), the court asserted that "[e]ven if the addition of enhanced warnings did constitute 'misbranding'" under federal law, state law could nevertheless require those enhanced warnings because FDA enforcement action seemed un-

likely. *Id.* at 953. And in *Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142 (C.D. Cal. 2010), the court found no "clear evidence" because there was "no evidence that the FDA took any action against either Wyeth or Glaxo SmithKline for 'misbranding' their products." *Id.* at 1158. These courts literally demand that companies be subjected to criminal proceedings before a preemption defense can succeed. *See* 21 U.S.C. § 331(a) (establishing criminal penalties for misbranding).

It is impossible to square these approaches with this Court's preemption jurisprudence. If *Wyeth*'s "clear evidence" standard means anything, it at least must be satisfied where FDA has rejected a previously proposed warning. That is "clear evidence" of the Agency's position at its most basic. And this straightforward approach provides an easily administered national standard that will allow manufacturers to sell their federally regulated products in all 50 states, with the label FDA requires, and without fear of runaway jury verdicts. Faced with the kind of unpredictable risk created by decisions like the SJC's, however, the only truly safe option for manufacturers is to stop selling their products in recalcitrant jurisdictions—even when FDA has determined that such products should be available to consumers, and despite this Court's admonition that "an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability." *Bartlett,* 133 S. Ct. at 2477.

II. THIS CASE IMPLICATES IMPORTANT AND RECURRING QUESTIONS ON THE

APPLICATION OF PREEMPTION PRINCIPLES IN THE OTC CONTEXT.

The practical impact of the SJC's approach is startling. Taken to its logical conclusion, the SJC's approach means that almost no FDA decision would receive preemptive effect; creative plaintiffs can always tweak a few words and then assert that FDA did not expressly reject the precise words later proposed at trial. And despite the respect to which FDA's decisions are due, the SJC's approach all-but-accuses the Agency of allowing its life-and-death decisions to turn on the identity of the petitioner, not on whether a Petition's request will save lives, prevent injury or disease, or promote public health in light of the competing considerations FDA must evaluate in this context. Based on that skewed view of FDA's approval process, the decision invites courts to second-guess FDA judgments. For that reason, granting certiorari here would allow this Court to resolve outstanding conflicts over FDA's role in approving drug labels, especially in the OTC context.

A. The SJC's Decision Conflicts With Other Courts' Views Of The Federal Regulatory Process.

It is hard to overstate the immense burdens that the SJC's approach would impose on FDA if left undisturbed. To successfully assert a preemption defense after FDA rejects a proposed warning, the manufacturer must either risk enforcement action by unilaterally adding the rejected warning and then asking FDA to reconsider its prior decision, or refile a duplicative Citizen Petition. Either way, FDA will

be forced to engage endlessly in the process of review-respond-and-repeat, no matter how obvious it is that FDA already studied the relevant scientific evidence and reached the resolution it deems optimal.

The resulting burden on FDA is intolerable given its public-health responsibilities. And it is inconsistent with the governing legal framework. The SJC's approach effectively demands that a manufacturer change its labeling to reflect previously rejected warnings despite the absence of any new evidence. That conflicts with the First Circuit's decision in *Celexa*, which recognized that federal law does not permit manufacturers to implement labeling changes unless they have new data or other relevant information that the Agency has not yet considered. 779 F.3d at 41-42 ("The CBE procedure is only available to make changes that, among other things, are based on 'newly acquired information.'") (quoting 21 C.F.R. § 314.70(c)(6)(iii)).

As a result, manufacturers may not initiate a label change simply because an earlier FDA decision responded only to a third-party's Citizen Petition or because FDA failed to provide an explanation that the manufacturer predicts will be sufficient to satisfy a recalcitrant court that is bent on letting plaintiffs' claims proceed to trial. Yet that is precisely what the SJC would force manufacturers to do. Given the SJC's view of the regulatory process, claims now can proceed in Massachusetts state courts that the First Circuit would reject under *Celexa*.

To the extent the SJC's decision allows an alternative—maintaining the same label but seeking a new decision based on the same evidence FDA al-

ready considered—it is no more defensible. Preemption analysis turns on what "the private party could independently do," not on its ability to "ask[] the FDA for help." *Mensing*, 131 S. Ct. at 2579. Moreover, letting state law force manufacturers to seek reconsideration of the Agency's prior decisions absent new data or information would impermissibly unleash "a deluge of information that [FDA] neither wants nor needs." *Buckman*, 531 U.S. at 351.

B. The SJC's Decision Undermines FDA's Regulatory Objectives In The OTC Context.

Finally, it bears emphasis that these concerns have special force in the OTC context. Like others, the court below apparently thought there is no harm in pressuring companies to add new warnings to their OTC labels and then seek FDA approval. Whatever merit that approach might have in *Wyeth*'s prescription-drug context, it is misplaced in the OTC context.

That is so because there is a critical difference between prescription-drug and OTC labeling—the former is directed to trained medical professionals, while the latter is designed to inform laypeople. When physicians are the relevant audience, erring on the side of over-warning carries a far lower risk of over-deterrence: We trust that trained medical professionals can make appropriate prescribing decisions even in the face of stark warnings that a product carries the remote risk of "life-threatening disease." As a result, putting pressure on companies to

change their labels first, and ask for FDA approval second, may not seem particularly dangerous.

The analysis is markedly different in the OTC context. When consumers are the target audience, FDA has the far more difficult task of ensuring that the label provides the optimal amount of information for a lay audience—enough to meaningfully inform them of significant risks, but not so alarming that it frightens them away from using a beneficial drug (particularly when the most alarming risks are so remote). After all, even "a truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision." *Dowhal*, 88 P.3d at 14. For that reason, FDA's determinations about which warnings to include on an OTC drug label represent "a ceiling as well as a floor." *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 904 (2000).

Particularly in the OTC setting, it would undermine the federal regulatory scheme to allow state tort law to pressure companies to warn consumers of every conceivable risk, no matter how remote. *See Dowhal*, 88 P.3d at 14 ("The mere existence of [a] risk ... is not necessarily enough to justify a warning; the risk of harm may be so remote that it is outweighed by the greater risk that a warning will scare consumers into foregoing use of a product that in most cases will be to their benefit."). Instead of promoting public safety, a system that pressures companies to add warning after warning—and then wait for FDA's decision—frustrates the very public-health

goals that undergird the FDCA's insistence that FDA has final say over OTC labeling content.

That concern is critical. FDA has long recognized that OTC product labeling which *contains more information* sometimes *communicates less information* because ordinary consumers can become "overwhelm[ed]" easily. 64 Fed. Reg. at 13255. As the Seventh Circuit thus explained in *Robinson*, forcing companies to include any conceivable risk (in increasingly alarmist tones) "would make label warnings worthless to consumers." *Robinson*, 615 F.3d at 869-70 (citing authorities on "information overload").

The record in this case establishes that FDA carefully crafted the warnings for OTC Children's Motrin® with a keen eye to those concerns, by identifying disease symptoms and instructing users "to stop taking the drug when symptoms that might have been caused by it appear," *Robinson*, 615 F.3d at 870, but deliberately omitted proposed language that would have shocked or confused consumers. In short, FDA's carefully crafted warning serves the "nuanced goal" of providing necessary information to consumers while avoiding information overload that fosters poor choices. *See Dowhal*, 88 P.3d at 15.

Even so, the SJC's decision pays no attention to the nuanced public-health objectives at issue in the OTC context. Instead, its narrow approach to preemption stands as a clear "obstacle to the accomplishment and execution of [FDA's] objectives" in the OTC context, *Geier*, 529 U.S. at 873 (quotation omitted), by undermining the Agency's measured efforts to avoid alarmist warnings that it viewed as counterproductive in this context.

CONCLUSION

For the foregoing reasons, the petition should be granted.

Respectfully submitted,

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October 8, 2015

APPENDIX

SUPREME JUDICIAL COURT OF
MASSACHUSETTS, PLYMOUTH

No. SJC–11677.

LISA RECKIS & ANOTHER[1]

Plaintiff,

v.

JOHNSON & JOHNSON & ANOTHER[2]

Submitted Dec. 1, 2014

Decided April 17, 2015

BOTSFORD, J. Samantha T. Reckis was seven years old in late 2003, when she developed toxic epidermal necrolysis (TEN), a rare but life-threatening skin disorder, after receiving multiple doses of Children's Motrin. Children's Motrin is an over-the-counter (OTC) medication with ibuprofen as its active ingredient, and is manufactured and sold by the defendants McNeil–PPC, Inc. (doing business as McNeil Consumer & Specialty Pharmaceuticals [McNeil]), and its parent company, Johnson & Johnson. The plaintiffs, Lisa and Richard Reckis, and their child, Samantha,[3] claim that Samantha developed TEN as a result of being exposed to

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[1] Richard Reckis. Both Lisa and Richard sued individually and as parents and natural guardians of their minor child, Samantha T. Reckis.

[2] McNeil–PPC, Inc., doing business as McNeil Consumer & Specialty Pharmaceuticals.

[3] Because all the plaintiffs share a last name, we refer to them by their first names in this opinion.

ibuprofen in the Children's Motrin that was administered to her, and that the warning label on the Children's Motrin bottle rendered the product defective because it failed to warn consumers adequately about the serious risk of developing a life-threatening disease from it. After a lengthy jury trial in the Superior Court, the jury found in favor of the plaintiffs, awarding general damages to Samantha and loss of consortium damages to each of her parents.

Before us is the defendants' appeal from the Superior Court judgment. They raise three claims: (1) the defendants were entitled to judgment as a matter of law because the plaintiffs' central claim of failure to warn is preempted by the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 et seq., as administered by the Federal Food and Drug Administration (FDA); (2) the defendants also are entitled to judgment as a matter of law because the plaintiffs failed to prove causation as a matter of law—in the defendants' view, the plaintiffs' causation witness, Randall Tackett, Ph.D., was unqualified to render the opinions on causation that he did, his opinions were not scientifically reliable in any event, and there was no other competent evidence on which the necessary element of causation could be based; and (3) the damages awarded to each of the plaintiffs were "grossly excessive" and unsupported by the record. For the reasons we shall discuss, we affirm the Superior Court judgment.

Background. We summarize the facts from the evidence presented at trial.

1. On the afternoon of November 28, 2003, seven year old Samantha had a fever and sinus congestion and, consequently, her father purchased a bottle of OTC Children's Motrin. The bottle was packaged inside a box, with identical warnings on the outside of the box and on the bottle. Richard read the warnings on each, and administered a dose of Children's Motrin to Samantha around 2 P.M. that day. Samantha then took a nap until approximately 10 P.M., at which point she woke still with a fever and congestion, and Richard gave her a second dose of Children's Motrin.[4]

The next morning, on November 29, Samantha woke with redness and a rash on her chest and neck, and a sore throat; she also had the same fever and congestion as she had had the night before. Richard gave her a third dose of Children's Motrin. Richard testified at trial that he would not have given Samantha the third dose had the drug's label warned that redness, rash, or blisters might lead to a life-threatening disease, or if the label had warned that these symptoms could be signs of Stevens–Johnson Syndrome (SJS) or TEN.[5] He further stated that he would have prevented others from administering additional doses of Children's Motrin to Samantha had these warnings been on the drug.

Around 9 A.M. on November 29, Richard telephoned Samantha's mother to tell her about Samantha's rash, and Lisa made an appointment for

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[4] Samantha had taken Children's Motrin once before, in October, 2002.

[5] Richard also testified, however, that he was not familiar with Stevens–Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) at the time.

Samantha to see her pediatrician.[6] When Richard brought Samantha to Lisa's home around noon that day to pick up Lisa on the way to the appointment, Samantha had a fever, nasal congestion, crusty eyes, cracked lips, and a rash. The pediatrician opined that Samantha had the measles, and told Richard and Lisa to treat Samantha with Motrin three times per day. Lisa gave Samantha another dose of Children's Motrin that evening after reading the warning label on the bottle. Lisa testified at trial that she would not have given this dose had the drug's label mentioned rash as a warning signal.

When Samantha woke up the next morning, on November 30, most of her body was covered in blisters. She could not open her eyes or mouth, and her lips were bleeding. Richard and Lisa took Samantha to the emergency room of Jordan Hospital (Jordan) where she received another dose of ibuprofen. When Samantha's condition worsened that day, she was transferred to Massachusetts General Hospital (MGH) and, shortly thereafter, to Shriners Hospitals for Children (Shriners) in Boston, where doctors diagnosed Samantha with TEN and informed Lisa and Richard that Samantha had a minuscule chance of surviving through the night. Tests administered at Jordan, MGH, and Shriners essentially ruled out a virus as the cause of Samantha's disease.

Samantha was put into a medically induced coma to ease her pain for approximately one month beginning on December 1, and was hospitalized for the next six months. During her hospitalization,

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[6] Richard and Lisa were separated at the time, and were divorced by the time of trial.

Samantha's TEN resulted in bloody secretions and affected approximately ninety-five per cent of her body's surface area; the top layer of her skin died and sloughed off. She suffered heart and liver failure. At one point, while Lisa cradled Samantha in her arms at the hospital, Samantha suffered a stroke followed shortly thereafter by an aneurysm. She also suffered a cranial hemorrhage that caused seizures, and underwent brain surgery. While in the hospital, she had only twenty percent of her lung capacity; falling below fifteen percent of lung capacity puts one at high risk of death. Her eyes were inflamed. Samantha became addicted to pain medications that were given to her to ease her discomfort, and she suffered visible withdrawal symptoms, shaking and shivering as she was weaned off the medications. Around the time of her release from the hospital in May of 2004, Samantha weighed approximately thirty-five pounds.

The jury heard conflicting expert testimony concerning whether Children's Motrin had caused Samantha's TEN. The plaintiffs' expert witness Randall Tackett testified that the medication did so, as did both Dr. Bonnie Mackool, the director of inpatient dermatology services at MGH and the director of dermatology at Shriners, who treated Samantha during her initial six-month hospitalization, and Dr. Stephen Foster, Samantha's treating ophthalmologist at the time of trial who had treated Samantha since that initial hospitalization. Other experts, including the defense witnesses Dr. Stanford T. Shulman and Dr. Maja Mockenhaupt, testified that ibuprofen had not caused Samantha's TEN.

After being released from the hospital in the spring of 2004, Samantha needed to eat through a feeding tube for two years, and required oxygen assistance at night for two years as well. On occasion, the feeding tube would become dislodged, resulting in pain. She returned to school in the fall of 2004 and repeated first grade; during that school year, Samantha's teacher had to carry her up and down stairs due to her small size, and Samantha needed to visit the school nurse every day to eat lunch through her feeding tube. At the time of trial in early 2013, Samantha was sixteen years old and weighed eighty-two pounds.

Between her initial release from MGH and Shriners in 2004 and trial, Samantha had been hospitalized several times with pneumonia and for trouble with her breathing, and she had had multiple bouts of bronchitis. She had scarring in her lungs. By 2011, Samantha's lungs had improved but they still functioned at less than half of their capacity, and she could not engage in any athletic activities. Samantha's pediatrician testified that, as a result of Samantha's low lung capacity, she will not be able to maintain a pregnancy.

Since 2004, Samantha has had more than twelve eye surgeries. Before a surgery conducted shortly before trial during which doctors implanted a prosthesis to replace the lens of the cornea in Samantha's left eye, Samantha was legally blind.[7]

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[7] Although there was a complication deriving from this surgery, the eye surgeon who performed it testified at trial that he was confident this problem could be addressed. However, while not part of the trial record, posttrial filings include an affidavit of the eye surgeon indicating that since trial, Samantha had undergone multiple surgeries to correct the problem, to no avail by that point, and would

Following this surgery, Samantha will be required to apply topical antibiotics to her eye often for the remainder of her life, and have her contact lens changed by a specialist each month. Samantha's right eye suffers from in-turned eye lashes that rub against her scarred cornea, resulting in mucus stimulation collecting on the cornea. To read, she has used a projector to enlarge the type, and she sits very near to the screen onto which the words are projected. She needs to press her nose to her telephone or the television to see what is on the screen of each.

At the time of trial Samantha was in the ninth grade. She was an honors student, but it took her much longer than other students to complete her homework. She enjoyed her coursework at school, liked to shop at the mall with friends, and often played video games. Samantha was close to her parents before developing TEN and remained so after it. She testified that she wants to attend college and study nursing, and that she hopes to work as a nurse at MGH.

Despite her optimism, Samantha suffers cognitive limitations, and her memory is not as sharp as it was before her illness. Due to her memory loss, she struggles to retain information, which makes completing her schoolwork a constant challenge. She will never be able to drive an automobile, and she remains dependent on others for assistance in her daily life. For the remainder of her life, she will be at increased risk for frequent hospitalizations, lung problems such as asthma and wheezing at a

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lose her left eye if surgical correction were ultimately to prove unsuccessful.

minimum, and further eye complications, such as glaucoma.[8] She also will always be at a great risk of illness and at a severe disadvantage in terms of fighting disease due to her pulmonary deficiencies and low body weight.

During the acute stage of Samantha's TEN and in the years that followed, her parents devoted themselves to caring for Samantha's many needs. They stayed with her throughout her hospitalization. Richard spent nights in a reclining chair, and Lisa slept in a room the size of a closet. They suffered significant distress in monitoring the progression of Samantha's disease and were often told during Samantha's hospitalization that she would not survive. Since then, Richard, who previously worked as a chef, took a job at a local gasoline station because the shorter hours permitted him to better tend to Samantha. In all, they have not been able to watch Samantha enjoy a normal childhood as a result of the numerous, significant, and constant challenges to her health.

2. The defendants manufacture and market the Children's Motrin brand of ibuprofen, which is a nonsteroidal anti-inflammatory drug (NSAID) used to treat minor aches and pains as well as fever.[9] In 1989, the FDA, which approves and regulates prescription and nonprescription medications, approved McNeil to sell pediatric prescription

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[8] See note 7, *supra*.

[9] At trial, the defendants disputed that Johnson & Johnson played a role in the manufacture of over-the-counter (OTC) Children's Motrin, and Johnson & Johnson moved for a directed verdict on this ground. The judge denied the motion. The jury answered separate special questions finding each defendant equally liable. The defendants do not raise any issue concerning Johnson & Johnson individually on appeal.

ibuprofen called Pedia Profen, and in 1995, McNeil obtained FDA approval to sell Children's Motrin as an OTC pediatric fever reducer and pain reliever.

TEN and SJS are severe disorders or diseases that attack the skin, resulting in a rash and a diffused eruption of blisters and significant damage to the mucosal membranes throughout the body, particularly the mouth, eyes, and genital and anal areas. SJS occurs where less than ten per cent of the body's surface is affected by the disorder, while TEN occurs where more than thirty per cent of the body's surface is so affected.[10] Both diseases can lead to scarring and infection; with TEN, the top layer of skin dies and the skin sloughs off, leaving raw areas that are predisposed to infection, a condition that can lead to death. SJS and TEN can cause blindness and significant damage to the respiratory and reproductive systems. According to the FDA, SJS has a mortality rate of five per cent, and TEN is fatal in some thirty per cent of cases.[11] The jury heard testimony from both parties' experts indicating that ibuprofen, the active ingredient in Children's Motrin, is associated with SJS and TEN.

3. When Samantha was given OTC Children's Motrin in 2003, the "warnings" section of the FDA-approved Children's Motrin label contained an "[a]llergy alert" that read as follows:

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[10] If between ten per cent and thirty per cent of the body's surface is affected by the skin reaction, the disease is classified as SJS/TEN.

[11] SJS and TEN are rare disorders or diseases. The Food and Drug Administration (FDA) estimated in 2006 that "the overall incidences of SJS and TEN range from 1.2 to 6 [cases] per million [persons] per year and 0.4 to 1.2 [cases] per million [persons] per year, respectively."

"Ibuprofen may cause a severe allergic reaction which may include:

* hives	* facial swelling
* asthma (wheezing)	* shock

The warnings section of the label also alerted consumers to "[s]top use and ask a doctor if ... an allergic reaction occurs" or if "any new symptoms appear." The label did not mention SJS or TEN, the possibility of skin reddening, rash, blisters, or the onset of a life-threatening disease.[12]

On February 15, 2005, a group that included physicians and Tackett[13] submitted to the FDA a petition concerning the relationship between ibuprofen and SJS and TEN (citizen petition).[14] The citizen petition requested the FDA to "conduct a risk assessment of [SJS] and [TEN] associated with the use of ibuprofen products" and to "require manufacturers of ibuprofen to amplify their prescription and [OTC] labeling to adequately warn" of the risks of SJS and TEN.[15] Specifically, the citizen petition requested two alterations to the OTC

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[12] However, the label of prescription Children's Motrin did warn at this time that Motrin may cause SJS and TEN.

[13] Randall Tackett, Ph.D., is a pharmacologist who was an expert witness for the plaintiffs at trial.

[14] An individual may file a petition with the FDA to request that it "issue, amend, or revoke a regulation or order, or ... take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.25(a)(2) (1989). See *In re Prograf Antitrust Litig.,* U.S. Dist. Ct., No. 1:11–md–2242–RWZ, 2012 WL 293850 (D. Mass. Feb. 1, 2012).

[15] The citizen petition included references to studies and literature that, according to the petition, indicated an association between ibuprofen and SJS and TEN. It also incorporated an analysis of reports of adverse reactions to ibuprofen, and a safety assessment of nonsteroidal anti-inflammatory drugs (NSAIDs) performed by the petitioners.

ibuprofen warning label. The first request was the inclusion of the following language in the "[w]arnings" section of the label:

"Serious Skin Reactions: Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including ... [SJS] and [TEN]. Seek immediate attention if any of these symptoms develop while taking ibuprofen" (emphasis added).

The second request was for the addition of the following new warning:

"Stop use and ask a doctor if: a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including" SJS and TEN.

In the alternative, the citizen petition requested that the FDA reconsider its approval of OTC pediatric ibuprofen products.

The FDA responded formally to the citizen petition in 2006. Before doing so, the agency engaged in what it termed "a comprehensive review of the risks and benefits" of ibuprofen, "including the risks of SJS and TEN," and in April of 2005, the FDA announced its request that manufacturers of OTC NSAIDs include warnings regarding symptoms that were associated with SJS and TEN, and specifically, "skin reddening," "rash," and "blisters.[16] In a June,

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[16] The updated warnings were to appear in the "[a]llergy alert" section of the OTC pediatric ibuprofen label, and were to read as follows:

"Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

2005, letter to McNeil, the FDA requested that McNeil revise the "[a]llergy alert" warning on OTC Children's Motrin to add warnings about these three symptoms.

The FDA's formal response to the citizen petition, dated June 22, 2006, acknowledged that "NSAIDs, including ibuprofen, are known to cause SJS and TEN," and that "[p]rompt recognition of the onset of symptoms, such as the appearance of rash or blisters on the skin, and withdrawal of the suspected drug can minimize the effects of SJS/TEN and improve prognosis." Accordingly, the FDA agreed with the petitioners that the labeling of OTC ibuprofen products such as Children's Motrin "should be improved to warn consumers about the risks of severe skin reactions associated with" such products. The FDA, however, also took the position that it was not useful for OTC ibuprofen labels "to include the specific terms SJS, TEN, ... Stevens–Johnson syndrome, and toxic epidermal necrolysis" because "most consumers are unfamiliar with these terms." Finally, the FDA declined to reconsider its stance on allowing the sale of OTC pediatric ibuprofen based on the grounds that "the incidence of SJS or TEN is not as great as cited" in the citizen petition, that "the overall benefit versus risk profile for ibuprofen products remains very favorable when they are used according to the labeled instructions," and that it is in the public health's interest "to maintain in the

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"*hives *facial swelling *asthma (wheezing)

*shock *skin reddening *rash *blisters"

"If an allergic reaction occurs, stop use and seek medical help right away."

pediatric OTC market a range of therapeutic options for the short-term relief of pain."

4. The plaintiffs filed their complaint in the Superior Court in January, 2007. The amended complaint, filed December 14, 2012, alleges negligence, breach of warranty, failure to warn of potentially lethal side effects of Children's Motrin, violation of G.L. c. 93A, loss of consortium, and negligent infliction of emotional distress.[17] Prior to trial, the defendants filed a motion for summary judgment claiming they were entitled to judgment because the plaintiffs' central cause of action based on failure to warn was preempted by the FDCA. Hedging their bets, they also filed a motion in limine to exclude evidence or argument at trial that the OTC Children's Motrin label should have warned of SJS or TEN by name, or of the possibility of the onset of a life-threatening disease, on the ground that any claim based on the defendants' failure to include these warnings was preempted. The trial judge denied both of these motions. The trial judge also denied the defendants' motion in limine seeking to exclude Tackett's opinion testimony that ibuprofen caused Samantha's TEN, rejecting the defendants' argument that he lacked the qualifications necessary to offer such an opinion.[18]

The case was tried in January and February, 2013. The jury answered special questions to the effect that Samantha's ingestion of Children's Motrin

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[17] In their amended complaint the plaintiffs effectively withdrew previous claims alleging defective design and manufacturing.

[18] The defendants subsequently challenged Tackett's testimony on the basis that he was not qualified to offer an opinion supporting a finding on specific causation in their motion for a directed verdict at trial. The judge denied the motion.

caused her TEN, and that both defendants negligently failed to provide adequate warnings in connection with Children's Motrin, causing harm to Samantha. The jury further found that both Lisa and Richard suffered a loss of consortium as a result of Samantha's injuries.[19] The jury awarded Samantha $50 million in compensatory damages, and awarded $6.5 million to each of Lisa and Richard for their loss of consortium.[20]

Following trial, the defendants filed motions for judgment notwithstanding the verdict and for a new trial in which they renewed their preemption argument, as well as their contention that Tackett lacked the proper qualifications to opine as to the cause of Samantha's TEN. The judge denied these motions in their entirety. The judge also denied the defendants' motion for remittitur, in which they argued that the jury's damage awards were excessive and unsupported by the evidence. The defendants filed a timely appeal in the Appeals Court, and we granted direct appellate review.[21]

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[19] With regard to breach of warranty, the jury found each defendant liable for rendering Children's Motrin defective due to inadequate warnings, and that this defect caused harm to Samantha. The plaintiffs' negligent infliction of emotional distress claim was withdrawn at trial and not submitted to the jury.

[20] After a jury-waived trial on the G.L. c. 93A claim, the judge found that the defendants knowingly or willfully engaged in unfair and deceptive acts or practices under c. 93A. Nevertheless, the judge found in favor of the defendants on the ground that the plaintiffs' c. 93A claim was barred by the permitted practices exemption. See G.L. c. 93A, § 3 ("Nothing in this chapter shall apply to transactions or actions otherwise permitted under laws as administered by any regulatory board or officer acting under statutory authority of the commonwealth or of the United States"). See also *Fleming v. Nat'l Union Fire Ins. Co.,* 445 Mass. 381, 389, 837 N.E.2d 1113 (2005).

[21] We acknowledge the amicus briefs submitted by The Consumer

Discussion. 1. *Preemption.* The defendants renew their argument that the plaintiffs' claim of failure to warn is preempted by the FDCA, and that the trial judge erred in denying them judgment as a matter of law on this ground.[22] Preemption "may be either expressed or implied, and 'is compelled whether Congress' command is explicitly stated in the statute's language or implicitly contained in its structure and purpose.'" *Gade v. National Solid Wastes Mgt. Ass'n,* 505 U.S. 88, 98, 112 S. Ct. 2374, 120 L.Ed.2d 73 (1992), quoting *Jones v. Rath Packing Co.,* 430 U.S. 519, 525, 97 S. Ct. 1305, 51 L.Ed.2d 604 (1977). Conflict preemption is a type of implied preemption; it occurs "where compliance with both federal and state regulations is a physical impossibility, ... or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" (quotations and citations omitted). *Gade, supra.* See *Wyeth v. Levine,* 555 U.S. 555, 588–589, 129 S. Ct. 1187, 173 L.Ed.2d 51 (2009) (Thomas, J., concurring in the judgment). See also *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.,* 951 F. Supp. 2d 695, 702–703 (D.N.J. 2013) (*Fosamax*).

The defendants contend that this is a classic case of conflict preemption, in that the warning the plaintiffs say would have made a difference—

Healthcare Products Association; American Association for Justice; Product Liability Advisory Council, Inc.; Massachusetts Bar Association and Massachusetts Medical Society; Massachusetts Trial Attorneys; and the Attorney General.

[22] In addition to raising their Federal preemption claim in their summary judgment motion and motion in limine, the defendants advanced the claim again in their motion for a directed verdict at the close of the plaintiffs' case, motion for judgment notwithstanding the verdict, and motion for a new trial, all of which the judge denied.

difference in the sense of changing the outcome by persuading Richard to cease giving any further doses of Children's Motrin to Samantha once the rash appeared after the second dose[23]—is one that the FDA has expressly rejected, thereby putting the defendants in the impossible position of having to comply with conflicting Federal and State requirements.[24]

The plaintiffs' argument fails. Section 379r is entitled, "[n]ational uniformity for nonprescription drugs," and it expressly preempts certain State requirements relating to the regulation of OTC drugs. See 21 U.S.C. § 379r(a) (2012) ("no State ... may establish or continue in effect any requirement ... that is different from or in addition to, or that is otherwise not identical with, a requirement under [the FDCA]"). The "savings clause" on which the plaintiffs rely, § 379r(e), begins with a heading stating, "[n]o effect on product liability law," and then provides: "*Nothing in this section* shall be

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[23] The defendants point to the following testimony of Richard:

Q.: "If this label that you had purchased the day before had said to beware of redness and rash because they might—redness, rash, blisters because they might be the pathway to a life-threatening disease—... [w]ould you have ever given Sammy that third dose of Motrin?"

A.: "Absolutely not."

Q.: "Now if it had said beware and keep an eye out for redness among the other things we've already read but redness, rash, blisters because this could be the warning sign of toxic epidermal necrolysis or Stevens Johnson Syndrome, would you ever have given Sammy that for a third dose?"

A.: "Absolutely not."

[24] The conflict between Federal and State law would exist because the FDA regulates OTC drug labels as a matter of Federal law, and a State jury verdict and judgment in this case constitutes State law.

construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State" (emphasis added). Thus, by its terms, the § 379r(e) savings clause frames its exemption from preemption with a reference to § 379r itself and, as a result, must be read in the context of § 379r as a whole and specifically the express preemption provision set out in § 379r(a).[25] The savings or exemption from preemption provided by § 379r(e), however, does not extend beyond the provisions of § 379r, and in particular does not preclude "the ordinary working of conflict pre-emption principles." See *Geier v. American Honda Motor Co.,* 529 U.S. 861, 869, 120 S. Ct. 1913, 146 L.Ed.2d 914 (2000). That is, even if the savings clause in § 379r(e) "removes tort actions from the scope of [an] express pre-emption clause" such as § 379r(a), the savings clause "does not foreclose ... the possibility that a federal [law] will pre-empt a state common-law tort action with which it conflicts," see *Geier, supra* at 869–870, 120 S. Ct. 1913, and principles of implicit conflict preemption would still bar the plaintiffs' claim if the result the plaintiffs sought would require the defendants to use a warning label that conflicted with FDA requirements. See *id.* at 871, 120 S. Ct. 1913 (without operation of ordinary preemption principles, "state law could impose legal duties that would conflict directly with federal regulatory mandates"). Accordingly, we interpret the savings clause to spare the plaintiffs' State law claim from express preemption by the FDCA that otherwise would result

[25] The additional subsections of 21 U.S.C. § 379r (2012) are not relevant to this discussion.

by virtue of § 379r(a), but the plaintiffs' claim remains susceptible to implicit conflict preemption.[26]

We turn to the defendants' conflict preemption claim. They argue that under the Supreme Court's decision in *Wyeth,* the plaintiffs' claim of failure to warn is preempted because exceptionally "clear evidence," *Wyeth,* 555 U.S. at 571, 129 S. Ct. 1187, exists that the FDA would not have approved the warning that the plaintiffs argue was called for, thus creating an impossible conflict between State tort law and the Federal regulatory requirements of the FDCA.

In *Wyeth,* the plaintiff prevailed in a products liability suit that included a claim of failure to warn relating to the warning label on a prescription drug manufactured by the defendant Wyeth. *Id.* at 559–560, 562, 129 S. Ct. 1187. The FDA had approved the label when it approved the defendant's supplemental new drug application. *Id.* at 561–562, 129 S. Ct. 1187.[27] The question before the Supreme Court was whether Federal law—specifically the

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[26] To the extent the plaintiffs construe a footnote in *Evans v. Lorillard Tobacco Co.,* 465 Mass. 411, 990 N.E.2d 997 (2013), to mean this court has determined as a general matter that conflict preemption principles do not come into play in the face of an express preemption savings clause in a Federal statute, the plaintiffs are mistaken. The footnote in question, see *id.* at 431 n. 11, 990 N.E.2d 997, discussed and concerned only the Federal Family Smoking Prevention and Tobacco Control Act. The footnote was not intended to, and did not, establish a general rule to govern the relationship between express statutory savings clauses and Federal principles of conflict preemption.

[27] The plaintiff's claim was that Wyeth's drug warning label "was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration" of the drug Phenergan "instead of the higher-risk IV-push method" used in the plaintiff's case. *Wyeth v. Levine,* 555 U.S. 555, 559–560, 129 S. Ct. 1187, 173 L.Ed.2d 51 (2009).

FDCA—preempted the plaintiff's State tort law claim of failure to warn concerning the prescription drug's warning label. *Id.* at 565, 129 S. Ct. 1187. Wyeth argued in favor of preemption on the ground that it was "impossible" for it to comply with both the State law warning duties that formed the basis of the plaintiffs' tort claims and the FDA's Federal labeling regulations. *Id.* at 568, 129 S. Ct. 1187. The Court acknowledged that typically a drug manufacturer may change a drug label only upon FDA approval of its supplemental application to do so, but noted that the FDA's "changes being effected" (CBE) regulation "provides that if a manufacturer is changing a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction,'" then the manufacturer "may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval." *Id.,* quoting 21 C.F.R. § 314.70(c)(6)(iii)(A). Noting that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times," *Wyeth, supra* at 570–571, 129 S. Ct. 1187, the Court concluded that once the risk of the "IV-push" injection method (see note 27, *supra*) was evident, Wyeth was obligated to warn of that risk, and "the CBE regulation permitted it to provide such a warning before receiving the FDA's approval." *Id.* at 571, 129 S. Ct. 1187. The Court recognized that "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation," but "absent *clear evidence* that the FDA would not have approved a change to Phenergan's label," it was not "impossible for Wyeth to comply with both federal and state requirements" (emphasis added). *Id.* at

571, 129 S. Ct. 1187. Accordingly, the plaintiff's claim was not preempted. *Id.* at 572–573, 129 S. Ct. 1187.[28]

Wyeth did not "define 'clear evidence,' so 'application of the clear evidence standard is necessarily fact specific.'" *Fosamax,* 951 F. Supp. 2d at 703, quoting *Dobbs v. Wyeth Pharms.,* 797 F. Supp. 2d 1264, 1270 (W.D.Okla.2011). In looking at the specific facts of this case, the first step is to identify what warnings the plaintiffs claim the defendants should have provided to give fair warning of the potentially deadly side-effects from Children's Motrin. The defendants argue that at trial the plaintiffs claimed that the Children's Motrin label should have mentioned SJS and TEN by name; the plaintiffs disagree that they did so, and we address this dispute, *infra.* However, the defendants are correct that the FDA's explicit rejection of the 2005 citizen petition's proposed inclusion of a specific mention of SJS or TEN by name on OTC ibuprofen drug labels because "most consumers are unfamiliar with these terms" provides the necessary "clear evidence" that the FDA would have rejected the addition of a warning on OTC ibuprofen's labeling that mentioned SJS or TEN by name. See *Robinson*

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[28] At oral argument in this case, the defendants' counsel noted a disagreement in the drug industry over whether the "changes being effected" (CBE) regulation applies to OTC drugs. Such a controversy was not discussed in the defendants' briefs, and they have not cited any cases or other authorities in support of the point. Because the defendants' preemption argument relies on Wyeth, and Wyeth incorporated the CBE regulation into its reasoning, we consider the CBE regulation as applicable to OTC drugs. Other courts have applied the CBE regulation in cases asserting failure to warn in relation to an OTC drug. See, e.g., *Newman v. McNeil Consumer Healthcare,* U.S. Dist. Ct., No. 10–CV–01541, 2012 WL 39793 (N.D.Ill. Jan. 9, 2012).

v. McNeil Consumer Healthcare, 615 F.3d 861, 873 (7th Cir.2010) ("The 'clear evidence' in this case is the agency's refusal to require a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do so in the submission [i.e., citizen petition] to which the agency was responding"). See also *Fosamax,* 951 F. Supp. 2d at 703 (FDA's denial of drug manufacturer's requested change to "[p]recautions" section of label soon after plaintiff's injury provided clear evidence FDA would have rejected change before injury occurred); *Dobbs v. Wyeth Pharms.,* 797 F. Supp. 2d at 1276–1277 (FDA rejected defendant drug manufacturer's proposed expanded cautions on drug label—"clear evidence" found).

The question whether Federal law preempts the plaintiffs' claim that the Children's Motrin's label should have warned of redness, rash, or blisters that might lead or be a "pathway" to a life-threatening disease is another matter. The defendants assert the FDA's response to the citizen petition demonstrates that, like the disease names "SJS" and "TEN," the FDA specifically rejected the request to require that OTC ibuprofen labels warn that rashes and blisters may lead to a "life-threatening" disease. We do not read the FDA to have done so. The FDA stated in its response the following:

"You[, the signers of the citizen petition,] recommend that FDA reconsider the OTC status of the pediatric formulation of ibuprofen or, at a minimum, add the following changes to ibuprofen OTC labeling:

• "In the *'Warnings'* of the labeling: 'Serious Skin Reactions: Ibuprofen may cause serious skin

reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate attention if any of these symptoms develop while taking ibuprofen.'

• "In the *'Stop use and ask a doctor if':* 'a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermonecrolysis.'

"...

"We agree that the labeling for OTC NSAIDs, including all ibuprofen products, should be improved to warn consumers about the risks of severe skin reactions associated with OTC ibuprofen products.... As a result, we have requested that manufacturers include under the *Allergy alert* subheading the symptoms associated specifically with SJS and TEN. We do not believe that it is useful to include the specific terms *SJS, TEN,* or *erythema multiforme, Stevens–Johnson syndrome,* and *toxic epidermal necrolysis* in the OTC label because most consumers are unfamiliar with these terms. In addition, effective OTC labeling communicates warning information in a manner that consumers can quickly and easily identify and understand. Consequently, we believe a description of symptoms is more appropriate. Therefore, prominently displayed under the *Allergy alert* subheading in the Drug Facts Label, the labeling will include:

- skin reddening
- rash
- blisters

"In addition, under the *Allergy alert* subheading, the labeling will state: 'If an allergic reaction occurs, stop use and seek medical help right away.' We believe that adding these symptoms to the *Allergy alert,* with advice to stop use and seek medical attention immediately, will alert and educate consumers to the nature of the allergic reactions associated with SJS and TEN. Further, we intend to continue our consumer education efforts regarding the safe and effective use of OTC pain relievers."

As just discussed, this response clearly stated that (1) the FDA rejected the proposal to place the actual names of the diseases mentioned—Erythema Multiforme, SJS, and TEN—on any OTC ibuprofen label; and (2) the FDA adopted the citizen petition proposal to list specific early symptoms of the diseases. But that is all that we find clear. The proposed language, "potentially life-threatening diseases," was part of the same sentence as, and immediately followed by, the names of the three diseases or conditions that the FDA specified it did not think proper for an OTC ibuprofen label. Accordingly, the FDA's decision not to request that manufacturers add a warning about life-threatening diseases could well have been merely a byproduct of its rejection of these requested warnings on the basis that they mentioned Erythema Multiforme, SJS, and TEN by name. Whether the FDA also would consider including a mention of life-threatening diseases, by itself, to be inappropriate and off limits on the OTC label is anybody's guess; certainly the

reason specified by the FDA for rejecting use of the disease names—consumer unfamiliarity—does not apply to use of such a phrase. See *Newman v. McNeil Consumer Healthcare,* U.S. Dist. Ct., No. 10–CV–01541, 2012 WL 39793 (N.D.Ill. Jan. 9, 2012) (discussing same portion of FDA response to same citizen petition: "The Citizen Petition did include phrases like 'serious skin reactions' and 'life-threatening diseases' and the FDA did not ultimately require such language, but the agency provided no reasoning for those particular decisions; therefore, conclusions regarding how those phrases and their alleged analogues were considered and evaluated by the FDA are speculative"). See also *Lofton v. McNeil Consumer & Specialty Pharms.,* 682 F. Supp. 2d 662, 677–678 (N.D. Tex. 2010).

Moreover, because the defendants were not involved in the submission of the citizen petition, the absence of the FDA's explicit rejection of the phrase "life-threatening diseases" or any rationale for the decision not to request that manufacturers add such a warning takes on increased significance. That is, even assuming for sake of argument that we could predict the FDA would have rejected a citizen petition proposal to add only this warning, that would not answer whether the FDA would have rejected the warning had it been sought by the defendants themselves. See *Schedin v. Ortho–McNeil–Janssen Pharms., Inc.,* 808 F. Supp. 2d 1125, 1133 (D. Minn. 2011) (FDA's decision not to seek label change "in the face of a Citizen's Petition, not supported by the [drug] manufacturer does not constitute clear evidence that the FDA would have *rejected* a label change proposed" by manufacturer [emphasis in original]). Cf. *Dorsett v. Sandoz, Inc.,*

699 F. Supp. 2d 1142, 1157 (C.D. Cal. 2010) FDA's rejection of warning requests in citizen petitions "constituted determinations that the warnings should not be *mandated;* they were not determinations that manufacturers could not choose to add warnings that they believed were scientifically substantiated" [emphasis in original]). This is so in part because "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept." *Wyeth,* 555 U.S. at 570, 129 S. Ct. 1187.[29][30]

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[29] The Court in *Wyeth* specifically suggested that "clear evidence" could be established by the FDA's rejection of a drug maker's attempt to give the warning underlying a claim of failure to warn, see *Wyeth,* 555 U.S. at 572, 129 S. Ct. 1187, but there was no evidence of such a rejection here. Contrast, e.g., *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.,* 951 F. Supp. 2d 695, 703 (D.N.J. 2013). This is not to say that the *Wyeth* standard of clear evidence can be satisfied only by the FDA's rejection of a manufacturer's request for an additional warning. Clear evidence that the FDA would have rejected a new warning can be shown in other ways, as indicated in this case: as discussed, the FDA's response to the 2005 citizen petition plainly rejected warnings that mentioned SJS and TEN by name.

[30] The Court in *Wyeth* also pointed out that the "FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Wyeth,* 555 U.S. at 578–579 & n. 11, 129 S. Ct. 1187. In light of the burden on the FDA, we are reluctant to infer that its response to the citizen petition conclusively rejected a warning regarding a life-threatening disease in the absence of a direct statement on the subject. This view is supported by the observation in *Wyeth* that claims of failure to warn under State law "uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly," and that they "also serve a distinct compensatory function that may motivate injured persons to come forward with information." *Id.* at 579, 129 S. Ct. 1187. Moreover, the savings clause in 21 U.S.C. § 379r(e) (2012) that exempts from express preemption products liability actions brought under State law, although not dispositive on the issue of conflict preemption, supports the general notion that products

In sum, "[i]mpossibility pre-emption is a demanding defense," *id.* at 573, 129 S. Ct. 1187, and we cannot glean from the FDA's response to the citizen petition, or from any other source in this record, clear evidence that the FDA would not have approved a warning on OTC ibuprofen labels stating that redness, rash, and blisters may lead to a life-threatening disease, so if an allergic reaction occurs, stop use and seek medical help right away. But because we have concluded that principles of conflict preemption would bar any claim of failure to warn advanced by the plaintiffs on the premise that the OTC Children's Motrin label should have warned of SJS or TEN by name, we must consider, and therefore turn to, the defendants' argument that the jury may have based its finding of liability on this preempted theory.

The defendants contend that the jury were free to decide liability on the basis of the preempted theory of failure to warn because (1) Richard testified he would have stopped administering Children's Motrin to Samantha once her rash appeared if the label had warned that a rash could be a sign of TEN, and (2) the trial judge declined to instruct the jury that they could not find the warning label inadequate for failing to mention SJS or TEN by name.[31] This argument is unavailing.

Certainly, where multiple theories were before a jury, at least one of which was improper, a new trial

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liability suits remain an important avenue for relief and indicates congressional intent that such actions are not to be prevented lightly.

[31] The defendants proposed that the judge instruct the jury that they could not find the defendants liable for failing to warn of SJS or TEN by name or for failing to warn of life-threatening diseases; the judge declined to give the instruction as proposed.

would be necessary if there is "no way of knowing on which basis the jury reached its verdict." *Rosado v. Boston Gas Co.,* 27 Mass.App.Ct. 675, 678, 542 N.E.2d 304 (1989). See *Slate v. Bethlehem Steel Corp.,* 400 Mass. 378, 384, 510 N.E.2d 249 (1987). Cf. *Evans v. Lorillard Tobacco Co.,* 465 Mass. 411, 445, 990 N.E.2d 997 (2013) ("Where we cannot ascertain on which theory the jury relied in finding causation, the jury's finding of liability as to negligence cannot stand"). This is not a case in which there is "no way of knowing" the basis for the jury's verdict; we are reasonably confident that the jury did not base liability on the defendants' failure to warn of SJS or TEN by name. For one, Richard testified that he had never heard of SJS or TEN when he gave Children's Motrin to Samantha, making it unlikely the jury would have credited his subsequent testimony that he would have stopped administering the drug to Samantha if the label had warned that a rash could be a sign of TEN. In addition, Lisa testified that if the warning label had mentioned rash as a warning signal, she would not have given Samantha the additional dose of Children's Motion when Richard brought Samantha to Lisa's house on November 29; Lisa did not mention SJS or TEN in connection with a warning. Moreover, the plaintiffs' trial counsel stated explicitly to the jury in his closing argument that the plaintiffs did *not* contend that the warning should have mentioned SJS or TEN by name;[32] he argued solely that the warning should have mentioned the

[32] Counsel told the jury: "Now, just to be clear, I mean, just to be clear what we say the label should have said, we don't take the position that it had to have the technical names of the diseases. That stuff. That doesn't happen because most people don't know what they are."

possibility that redness, rash, or blisters could lead to a life-threatening disease. In these circumstances, although it is theoretically possible that the jury reached their verdict on the basis of the defendants' failure to warn about the possible occurrence of SJS and TEN, the likelihood appears very slim, and we find no reason to disturb the jury's verdict on preemption grounds.

2. *Expert testimony.* The defendants argue that they were entitled to judgment as a matter of law on the ground that the causation evidence essential to the plaintiffs' case came from Dr. Randall Tackett, a pharmacologist, who offered the testimony without the necessary qualifications or a proper foundation.

We start on common ground with the defendants: expert testimony is required to establish medical causation.[33] See *Canavan's Case,* 432 Mass. 304, 316, 733 N.E.2d 1042 (2000). "'The crucial issue,' in determining whether a witness is qualified to give an expert opinion, 'is whether the witness has sufficient "education, training, experience and familiarity" with the subject matter of the testimony.'" *Commonwealth v. Frangipane,* 433 Mass. 527, 533, 744 N.E.2d 25 (2001), quoting *Commonwealth v. Richardson,* 423 Mass. 180, 183, 667 N.E.2d 257 (1996). With regard to the adequacy of the methodology supporting expert testimony, a "party seeking to introduce scientific evidence may lay an

[33] Medical causation has two components, both of which require expert opinion evidence. See *Kerlinsky v. Sandoz Inc.,* 783 F. Supp. 2d 236, 240 (D. Mass. 2011) ("an expert opinion on medical causation must contain two elements—general causation, i.e., that the drug *can* cause the injury, and specific causation, i.e., that the drug *did* cause the injury in this case" [emphasis in original]). Specific causation is the focus of the defendants' challenge here.

adequate foundation either by establishing general acceptance in the scientific community or by showing that the evidence is reliable or valid through an alternate means." *Canavan's Case, supra* at 310, 733 N.E.2d 1042. See *Commonwealth v. Lanigan,* 419 Mass. 15, 26, 641 N.E.2d 1342 (1994). In the end, a "trial judge has wide discretion to qualify an expert witness and to decide whether [a] witness's testimony should be admitted," and we will reverse a judge's decision to admit expert testimony "only where it constitutes an abuse of discretion or other error of law." *Frangipane, supra.* See *Canavan's Case, supra* at 312, 733 N.E.2d 1042. The defendants contend that Tackett was unqualified to render an opinion as to specific medical causation in Samantha's case because as a pharmacologist rather than a medical doctor, he has never diagnosed or treated a patient with TEN. The trial judge concluded otherwise, and we find no abuse of discretion in his doing so.

Tackett testified that he is a professor of pharmacology and toxicology at the University of Georgia's College of Pharmacy, and a former chair of its department of pharmacology and toxicology; he has taught these subjects there for three decades. Pharmacology, Tackett explained, involves the study, at the molecular level, of how a drug is metabolized and absorbed by the body, including how the drug is distributed once ingested and how particular dosages of drugs may lead to certain side effects. Toxicology, in turn, is primarily concerned with the adverse, or toxic, effects of a drug.

Tackett has a bachelor's degree in biology, and a master's degree and doctorate in pharmacology and

toxicology. He has written numerous peer-reviewed or refereed publications, primarily on pharmacology and toxicology. He has taught courses (forensic pharmacy and advanced therapeutics) that focus on the interactions of drugs with the human body. He has taught courses on NSAIDs as well. He also is experienced in reviewing medical records to determine the effects of a drug because doing so is a component of pharmacology and toxicology, and he has served as a peer-reviewer of papers written by physicians. He has not treated a patient with SJS or TEN or published an article on these diseases, but he was instructed on TEN during his training, and at the time of trial he had read a majority of the scientific literature concerning the causes of SJS and TEN.

The judge was entitled to credit Tackett's testimony about the depth and scope of his education, training, and experience in determining the manner in which drugs adversely affect the human body, and could also credit Tackett's testimony that he has considerable experience in reviewing patient medical records in order to determine the effects of a drug on the body. In light of the evidence of Tackett's qualifications, we find no error in the judge's ruling that Tackett was qualified to render an opinion on whether ibuprofen specifically caused Samantha's TEN despite the fact that he was not a physician treating TEN patients. See *Allen v. Martin Surfacing,* 263 F.R.D. 47, 57–58 (D.Mass.2009) (neurotoxicologist qualified to offer expert testimony as to specific medical causation despite lacking medical degree). See also *Frangipane,* 433 Mass. at 533–535, 744 N.E.2d

25.[34][35] We note also that Tackett's specific causation opinion was in accord with that of Samantha's treating physicians who testified at trial. Dr. Bonnie Mackool, a dermatologist, and Dr. Stephen Foster, an ophthalmologist, each of whom treated Samantha and examined her extensively, testified that ibuprofen had caused her to develop TEN. In addition, the jury heard evidence that the medical resident who examined Samantha upon her initial admission to MGH in 2003 indicated that Samantha's disease was caused by ibuprofen.

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[34] The defendants rely on *Commonwealth v. Frangipane,* 433 Mass. 527, 744 N.E.2d 25 (2001), for the proposition that Tackett was unqualified to testify as to specific causation, but the reliance is misplaced. In that case, a prosecution for rape of a child, we concluded that the trial judge had acted within his discretion in permitting a social worker called as an expert witness by the Commonwealth to offer opinion evidence on dissociative memory loss, recovered memory, and delayed disclosure among sexually abused children, based on the witness's extensive training, education and experience in the field; that she was not a medical doctor or psychologist did not "alter this conclusion." See *id.* at 527, 530–531, 533–535, 744 N.E.2d 25. We also concluded, however, that the witness was not competent, and should not have been permitted, "to testify about *how* a trauma victim stores and retrieves, or dissociates, a traumatic memory because the witness's testimony on these issues involved pronouncements concerning the physical functioning of the brain, a scientific and medical matter on which the Commonwealth failed to establish that the witness was qualified to testify" (emphasis in original). *Id.* at 535, 744 N.E.2d 25. Unlike the social worker witness in *Frangipane,* however, Tackett's education, training, and experience as a pharmacologist and toxicologist did encompass the science of how a drug, such as ibuprofen, produces adverse effects on the body.

[35] Our conclusion that Tackett was qualified to testify as to specific medical causation is in accord with other courts that have considered his qualifications to testify to an opinion that Motrin caused SJS or TEN. See *Wolfe v. McNeil–PPC, Inc.,* 881 F. Supp. 2d 650, 659 (E.D. Pa. 2012) (finding Tackett qualified to testify as to causation on basis of his experience as pharmacologist, "notwithstanding his lack of a medical degree"); *Lofton v. McNeil Consumer & Specialty Pharms.*, U.S. Dist. Ct., No. 3:05–CV–1531–LBH, 2008 WL 4878066 (N.D. Tex. July 25, 2008).

We turn to the defendants' argument that Tackett had no foundation for what the defendants refer to as his "third dose" opinion—that is, according to the defendants, the opinion that Samantha would not have contracted SJS or TEN if, once her rash appeared, she had not received the third dose of Children's Motrin.[36] The defendants contend that the "third dose" theory was an essential component of causation in the plaintiffs' claim of failure to warn, but was not medically or scientifically valid and not supported by medical literature.[37]

It is true that the plaintiffs' claim of failure to warn was premised in substantial part on Richard's testimony that he would not have given Samantha more Children's Motrin once her rash appeared had the drug's label warned that redness, rash, or blisters might lead to a life-threatening disease.[38]

That is, the omitted warning underlying the plaintiffs' claim became relevant to those caring for Samantha only once she woke up with a rash on the

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[36] The plaintiffs assert that the defendants did not object at trial to the foundation for Tackett's opinion that Samantha would not have contracted TEN had she not received any ibuprofen after suffering a rash. Accordingly, they argue, the defendants have waived this issue on appeal. The trial judge, however, recognized the defendants' continuing objection to, among other things, a lack of foundation for Tackett's testimony regarding specific medical causation. In the circumstances, we decline to find a waiver.

[37] As we discuss *infra,* this "third dose" theory is more accurately described as a "second dose" opinion because Tackett's testimony primarily conveyed an opinion that Samantha would not have contracted TEN had she received only the first two doses of Children's Motrin, and not the three subsequent doses. To avoid quibbles about numbers, we will refer to this as Tackett's "dose opinion."

[38] Richard also testified that he would have prevented others from giving Children's Motrin to Samantha once her rash appeared had the drug's label warned of the significance of a rash.

morning of November 29, the same morning that Richard gave her the third dose of Children's Motrin. To prevail on their claim of failure to warn, the plaintiffs had to establish that the lack of this warning caused Samantha's harm because its omission resulted in Samantha receiving more ibuprofen than she otherwise would have, resulting, ultimately, in TEN. See *Laaperi v. Sears, Roebuck & Co.,* 787 F.2d 726, 729 (1st Cir. 1986) ("the failure to warn of hazards associated with foreseeable uses of a product is itself negligence, and if that negligence proximately results in a plaintiff's injuries, the plaintiff may recover"; applying Massachusetts law); *Jones v. Walter Kidde Portable Equip.,* 16 F. Supp. 2d 123, 125 (D. Mass. 1998) (claim of failure to warn requires establishing causation through evidence indicating that if additional "warnings had been given and heeded, the outcome would have been different"; applying Massachusetts law). Accordingly, we agree with the defendants that Tackett's dose opinion, coupled with Richard's testimony, was an important step in establishing that an adequate warning on the Children's Motrin label about the significance of a rash would have prevented Samantha from receiving more ibuprofen and developing a full-blown case of TEN.

We are not convinced, however, that to establish liability it was essential for the plaintiffs to show that the third dose of Children's Motrin administered to Samantha, as opposed to the fourth or fifth dose, caused her to develop TEN. In 2003, when the warning on the Children's Motrin label that the plaintiffs argue should have been present was not, there appears to have been a general unfamiliarity about the significance of Samantha's rash. Thus, in

addition to the third dose of Children's Motrin administered by Richard, Samantha's pediatrician ordered continued treatment with the Children's Motrin despite the presence of her rash, resulting in Lisa administering a fourth dose to Samantha,[39] and Samantha was administered a fifth dose of ibuprofen the next day in the Jordan Hospital emergency department. Therefore, the plaintiffs could prevail on the issue of causation through evidence that any or all of the three doses administered to Samantha after she contracted a rash caused her to develop TEN and, thus, that an adequate warning to stop administering the drug upon the presence of a rash more likely than not would have resulted in a different outcome. See *Jones,* 16 F. Supp. 2d at 125. In this regard, Dr. Foster, Samantha's treating ophthalmologist, testified that Samantha did not have TEN after receiving the first two doses of Children's Motrin, but that her TEN symptoms materialized after the administration of the third dose. And Dr. Stanford T. Shulman, an expert witness of the defense, testified that "one or two doses of a drug like Motrin" cannot "trigger such a severe disease" as Samantha's TEN.

In any event, we cannot agree with the defendants that Tackett's dose opinion was incompetent and therefore inadmissible. Tackett based his testimony, generally, on his review of Samantha's medical records, including those from MGH and Shriners, as well as his awareness and working knowledge of relevant scientific literature.

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[39] As previously mentioned, Lisa testified that she would not have given Samantha the fourth dose of Children's Motrin had the label warned to discontinue use upon the appearance of a rash.

See *Canavan's Case,* 432 Mass. at 314–315, 733 N.E.2d 1042 (expert scientific opinion must be based on relevant literature or other indicia of reliability). After opining that ibuprofen caused Samantha's TEN, Tackett testified that had Samantha received only two doses of Children's Motrin, her illness would not have progressed to TEN. It is true, as the defendants note, that Tackett agreed that the scientific literature does not specifically support an opinion that had Samantha ingested only two doses of Children's Motrin, she probably would not have contracted TEN. However, Tackett's opinion testimony appeared to vary somewhat during his lengthy appearance as a witness and, although he did testify at one point that the third dose of Children's Motrin caused the disease, the thrust of his opinion testimony, as we read it, was that Samantha would not have contracted TEN had she received only the first two doses of Children's Motrin, and not the third, fourth, and fifth doses after her rash appeared. This opinion appears to find some support, as Tackett stated, in the literature, which recognizes that prompt withdrawal of the drug causing TEN symptoms leads to a better prognosis for the patient.[4040] Tackett's testimony indicated as

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[40] The FDA recognized in its response to the citizen petition that "[p]rompt recognition of the onset of symptoms [of SJS and TEN], such as the appearance of rash or blisters on the skin, *and withdrawal of the suspected drug can minimize the effects of SJS/TEN and improve prognosis* " (emphasis added). Furthermore, one of the defendants' expert witnesses in this case, Dr. Maja Mockenhaupt, has written that with regard to treating SJS and TEN the causative drug "should be rapidly identified and withdrawn." Mockenhaupt, Severe Drug–Induced Skin Reactions: Clinical Pattern, Diagnostics and Therapy, 7 JDDG 142, 142 (2009).

Additionally, Tackett referenced in his testimony a study that examined the effect of the withdrawal of a causative drug on patients

much, in that he stated that a "basic pharmacology tenet" holds that "if you keep giving a drug that's producing a toxic effect, it's going to amplify or make that toxic effect worse," and that stopping the causative drug allows the body to metabolize it and rid itself of the drug.[41]

Based on the state of the knowledge in the field concerning early withdrawal of causative drugs, see note 40, *supra,* the judge did not abuse his discretion

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who were diagnosed with SJS or TEN. See Garcia–Doval, Le Cleach, Bocquet, Otero, & Roujeau, Toxic Epidermal Necrolysis and Stevens–Johnson Syndrome: Does Early Withdrawal of Causative Drugs Decrease the Risk of Death?, 136 Arch. Dermatol. 323 (2000). This study selected patients diagnosed with SJS or TEN who had taken a drug believed to have caused their disease. *Id.* at 324. For purposes of the study, patients "were determined to have stopped [causative] drug administration early if the last dose of the causative drug was administered no later than the same day that a definite sign of TEN or SJS appeared," such as a blister or skin erosion. *Id.* The study revealed a better mortality rate among patients who stopped ingesting the causative drug early as opposed to those who stopped after the day on which a sign of SJS or TEN appeared. *Id.* at 324–325. The defendants contend that because each patient in this study was diagnosed with SJS or TEN at the outset, the study cannot support Tackett's opinion that ceasing administration of ibuprofen to Samantha after the second dose would have prevented her disease from worsening into TEN. We agree that the study cannot explicitly support Tackett's opinion, but the study's conclusion that "early withdrawal of the causative drug(s) is associated with a better prognosis for patients with TEN or SJS," *id.* at 327, provides general support for the notion that ceasing administration of Children's Motrin to Samantha sooner rather than later would have improved her prognosis.

[41] Tackett's dose opinion also must be considered in light of his unchallenged testimony that a diagnosis of TEN simply represents a determination that over thirty per cent of a person's body has been affected by the adverse skin disorder; an opinion that Samantha's condition would not have developed into TEN if only two doses of Children's Motrin had been administered in effect states a view that over thirty per cent of her body would not have become affected—not an opinion that Samantha would not have been ill.

in determining that Tackett's testimony was reliable and admissible. See *Palandjian v. Foster,* 446 Mass. 100, 111, 842 N.E.2d 916 (2006) (trial judge "has broad discretion to determine how to assess the reliability of expert testimony"). Cf. *Vassallo v. Baxter Healthcare Corp.,* 428 Mass. 1, 12–13, 696 N.E.2d 909 (1998) (judge did not err in admitting expert testimony that implants cause disease, despite lack of epidemiological study specifically supporting testimony, where causation opinion was based on, among other things, other relevant studies).

In any event, we have found Tackett qualified to testify as to specific medical causation. The defendants' criticisms of his dose opinion essentially go to the basis of his opinion, and affect the weight of the opinion rather than its admissibility.[42] See generally *Commonwealth v. Crouse,* 447 Mass. 558, 569, 855 N.E.2d 391 (2006). The defendants extensively cross-examined Tackett as to the basis of his dose opinion, and specifically as to whether the literature on which Tackett relied for his opinion was, in fact, supportive. See *Higgins v. Delta Elevator Serv. Corp.,* 45 Mass. App. Ct. 643, 648, 700 N.E.2d 833 (1998), quoting *Lanigan,* 419 Mass. at 26, 641 N.E.2d 1342 ("The judge's ruling 'is not final on the reliability of the [expert] opinion evidence, and the opponent of that evidence may challenge its validity before the trier of fact' ").

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[42] Accordingly, the judge appropriately instructed the jury that they had the prerogative to determine whether to accept the opinions of expert witnesses. See *Higgins v. Delta Elevator Serv. Corp.,* 45 Mass.App.Ct. 643, 648–649, 700 N.E.2d 833 (1998).

3. *Damages.* Last, the defendants challenge the jury's awards of damages.The jury awarded a total of $50 million in compensatory damages to Samantha as a general award of damages; although instructed on pain and suffering, future medical expenses, and loss of future earning capacity as categories of damages Samantha was entitled to have them consider, the jury were not asked to itemize or specify what portion, if any, of the total award represented damages for each or any of these categories. The jury also awarded $6.5 million to each of Samantha's parents for loss of consortium. As noted at the outset, the defendants moved for remittitur on the ground that the awards of damages were not supported by evidence in the record. The judge denied the motion, concluding that the evidence at trial supported the jury's total award, which, in the judge's view, was "not greatly disproportionate to the injuries proven."

"[A]n award of damages must stand unless ... to permit it to stand was an abuse of discretion on the part of the court below, amounting to an error of law." *Labonte v. Hutchins & Wheeler,* 424 Mass. 813, 824, 678 N.E.2d 853 (1997), quoting *Mirageas v. Massachusetts Bay Transp. Auth.,* 391 Mass. 815, 822, 465 N.E.2d 232 (1984). "It is an error of law if 'the damages awarded were greatly disproportionate to the injury proven or represented a miscarriage of justice.'" *Labonte, supra,* quoting *doCanto v. Ametek, Inc.,* 367 Mass. 776, 787, 328 N.E.2d 873 (1975). Damages are also excessive when they are "so great ... that it may be reasonably presumed that the jury, in assessing them, did not exercise a sound discretion, but were influenced by passion, partiality, prejudice or corruption." *Bartley v. Phillips,* 317

Mass. 35, 41, 57 N.E.2d 26 (1944), quoting *Coffin v. Coffin,* 4 Mass. 1, 43 (1808). However, "[a]buse of discretion in granting or refusing a new trial" on the ground of excessive damages "can so seldom be found that actual instances in which this court has set aside the action of the trial judge ... are almost nonexistent, and it has repeatedly been stated that occasions when this court can do so are exceedingly rare." *Loschi v. Massachusetts Port Auth.,* 361 Mass. 714, 715, 282 N.E.2d 418 (1972), quoting *Hartmann v. Boston Herald–Traveler Corp.,* 323 Mass. 56, 61, 80 N.E.2d 16 (1948). See *Blake v. Commissioner of Correction,* 403 Mass. 764, 771, 532 N.E.2d 671 (1989) ("We do not substitute our judgment for that of the trial judge who saw the witnesses").

a. *Award of damages to Samantha.* As a general matter, Samantha was "entitled to compensation for all damages that reasonably are to be expected to follow, but not to those that possibly may follow" the injuries she suffered. *Donovan v. Philip Morris USA, Inc.,* 455 Mass. 215, 223, 914 N.E.2d 891 (2009), quoting *Pullen v. Boston Elevated Ry.,* 208 Mass. 356, 357, 94 N.E. 469 (1911). Although they did not request the jury to be asked to specify separate amounts for future medical expenses, impairment of future earning capacity, and pain and suffering, the defendants' challenge on appeal focuses on each of these categories separately, and we consider them separately.

i. *Future medical expenses.*[43] The defendants assert that the trial evidence here (1) presented for the most part possibilities, not probabilities, of types

[43] The parties stipulated to approximately $810,000 in past medical expenses.

of future medical expenses Samantha might incur, and possibilities are an insufficient basis for an award, see *Donovan,* 455 Mass. at 223, 914 N.E.2d 891; and (2) in any event, even with probable future medical expense categories, failed to present any evidence—"dollars and cents evidence"—of what the future medical expenses were reasonably likely to be.

The defendants' argument suffers from two fatal flaws. The first is the defendants' failure to request that the jury be instructed to consider the discrete categories of damages separately. Since there is no way of knowing whether the jury did, in fact, include any amount for future medical expenses in their award, a claim premised on the assumption that they did can go nowhere; certainly the defendants' way around the problem of the missing information, which is to assume that the entire award of $50 million was for future medical expenses and then to assert that there was insufficient evidence to support such an award, does not provide a permissible solution. See *Dalessio v. Dalessio,* 409 Mass. 821, 830, 570 N.E.2d 139 (1991), *S.C.,* 413 Mass. 1007, 604 N.E.2d 676 (1992) (where jury returned general verdict it was unknown "exactly how the jury calculated their award or exactly how much of the total award was meant to compensate" for pain and suffering as opposed to other compensatory damages). Second, central to the defendants' argument is the assertion that there was insufficient evidence introduced at trial on which the jury could permissibly fashion an award to cover future medical expenses. But the defendants never challenged the absence or insufficiency of such evidence through a motion for a directed verdict on this ground and did not include this ground in their motion for judgment

notwithstanding the verdict. The plaintiffs argue correctly that the defendants have waived this claim. See *Shafir v. Steele,* 431 Mass. 365, 371 & n. 13, 727 N.E.2d 1140 (2000) (defendant waived objection to damages awarded for claim of interference with contract where he had not raised objection in motion for directed verdict; defendant also waived claim that judge erred in allowing jury to consider particular theory of measuring damages where he had not objected to instruction on this ground).[44]

ii. *Impairment of future earning capacity.* For the same reasons, the defendants' arguments concerning damages for impairment of future earning capacity also must be rejected: the jury's award of general damages offers no insight into whether they awarded

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[44] We note that the record does contain evidence, such as the testimony of treating doctors, as to Samantha's reasonably expected future medical expenses—e.g., medical expenses for monitoring her pulmonary system, monthly ophthalmologist appointments, periodic eye surgeries necessitated by her in-turned eyelashes, and likely hospitalizations due to her reduced lung function and low body weight. There was testimony that Samantha's medical concerns will follow her for her life, which, at the time of trial, was expected to last some sixty-six more years. That future medical expenses "cannot always be foretold with exactness is a fact which the jury have to deal with in determining what ... expense reasonably will follow as distinguished from what possibly may follow." *Donovan v. Philip Morris USA, Inc.,* 455 Mass. 215, 223, 914 N.E.2d 891 (2009), quoting *Pullen v. Boston Elevated Ry.,* 208 Mass. 356, 357–358, 94 N.E. 469 (1911).

On the issue of what anticipated future medical expenses might cost, although a plaintiff may offer evidence of future medical expenses through expert testimony, see *Harlow v. Chin,* 405 Mass. 697, 714–715, 545 N.E.2d 602 (1989), we have held that "[h]ospital records and the testimony of physicians" as to "anticipated future services permit[ ] the jury to use their judgment to award more than nominal amounts" as future medical expenses. *Bencosme v. Kokoras,* 400 Mass. 40, 44–45, 507 N.E.2d 748 (1987). See *VanAlstyne v. Whalen,* 15 Mass.App.Ct. 340, 347 n. 1, 445 N.E.2d 1073 (1983), *S.C.,* 398 Mass. 1004, 495 N.E.2d 837 (1986).

any amount for loss of future earning capacity and, if they did, what that amount was; and the absence of any challenge (e.g., a motion for a directed verdict) to the purported insufficiency of the evidence on this issue serves to waive the defendants' claims in any event.[45]

iii. *Pain and suffering.* As they did with the future medical expenses, the defendants again assume that the jury's entire award of $50 million in general damages represented pain and suffering damages, and they again assert that such a sum is excessive and "greatly disproportionate to the injury proven." See *Labonte,* 424 Mass. at 824, 678 N.E.2d 853. For reasons previously stated, we do not accept the defendants' governing assumption, but even were we to do so, we would disagree with their claim of excessiveness. It is unnecessary to recount again a full litany of Samantha's injuries, but the most severe of her injuries bear repeating in evaluating the amount of the award. As a result of having TEN, the seven year old Samantha suffered lesions

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[45] Insofar as the jury may have included some damages for loss of future earning capacity in their award, we add the following. Although, as the defendants point out, Samantha and her parents testified that she plans to attend college and become a hospital nurse, the jury could reasonably infer that despite Samantha's commendable optimism, her health will not allow her to pursue her chosen career in nursing or in any number of other occupations. See *Halnan v. New England Tel. & Tel. Co.,* 296 Mass. 219, 222, 5 N.E.2d 209 (1936). Instead, the evidence at trial regarding Samantha's lasting injuries and her appearance on the witness stand allowed the jury, "with their knowledge of practical affairs," to "measure the probable extent of the impairment of [Samantha's] earning capacity." See *Cross v. Sharaffa,* 281 Mass. 329, 331, 183 N.E. 838 (1933). The "assessment of damages for impairment of earning capacity rests largely on the common knowledge of the jury, sometimes with little aid from evidence." *Griffin v. General Motors Corp.,* 380 Mass. 362, 366, 403 N.E.2d 402 (1980).

(blisters) all over her body and lost the top layer of her skin (over ninety-five percent of it), substantially the same as for a severe burn victim; she was hospitalized for six months, where she needed to be placed in a medically induced coma for a full month to deal with the pain; while in the hospital, she suffered liver and heart failure, a stroke, seizures, and a cranial hemorrhage, and had only twenty per cent of her lung capacity; upon discharge she was required to eat through a feeding tube for two years and required oxygen every night for the same period of time; at the time of trial, she weighed just eighty-two pounds as a sixteen year old; she is legally blind;[46] her short-term memory is damaged; her lung capacity remains significantly impaired, and she will never be able to carry a child as a result; and she faces hospitalizations and limitations for the remainder of her life.

To be sure, Samantha's parents testified about her remarkable ability to endure these injuries while maintaining a positive outlook and prospects for the future. Samantha herself testified to her belief that she will lead a "great life." The jury could applaud this optimism but nevertheless reasonably infer from the significant extent of Samantha's past pain and suffering, and the state of her health, that she will likely experience pain and suffering throughout her life. See *Pemberton v. Boas,* 13 Mass.App.Ct. 1015, 1018, 433 N.E.2d 490 (1982) (upholding damages award where "[f]actors which would have warranted a lesser amount of damages were fully explored

[46] As mentioned, see note 7, *supra,* the corneal implant Samantha received has required many surgeries to try to correct problems interfering with the implant's success, so far unsuccessfully.

before the jury and apparently rejected by them"). Accordingly, we cannot say that the jury's award is "greatly disproportionate" to Samantha's grave injuries. See *Labonte,* 424 Mass. at 824, 678 N.E.2d 853. See also *Bartley,* 317 Mass. at 40, 57 N.E.2d 26 (damages may be "incapable of computation" and, thus, dependent on "judgment of the fact-finding tribunal in appraising suffering and deprivation and translating them into a compensatory sum").[47]

b. *Loss of consortium damages.* Finally, we decline to disturb the jury's awards to Lisa and Richard for loss of consortium.[48] In explaining the parameters of loss of consortium of a child, we have stated that parents may recover for "loss of filial society if they can show that [their child's] injuries are of such severity and permanence as to render [her] physically, emotionally, and financially dependent on them and that, as a result, their lives have been significantly restructured and their expectations of enjoying those experiences normally shared by parents and children have been seriously impaired." *Monahan v. Methuen,* 408 Mass. 381, 388–389, 558 N.E.2d 951 (1990), quoting *Norman v. Massachusetts Bay Transp. Auth.,* 403 Mass. 303, 316, 529 N.E.2d 139 (1988) (Liacos, J., dissenting). It is difficult to imagine how Lisa and Richard's lives could have been more "significantly restructured" as

---

[47] We decline the invitation of the parties to engage in the "dangerous game" of comparing the verdict in this case to that in other personal injury cases. See *Griffin v. General Motors Corp.,* 380 Mass. 362, 371, 403 N.E.2d 402 (1980).

[48] "The parents of a minor child or an adult child who is dependent on his parents for support shall have a cause of action for loss of consortium of the child who has been seriously injured against any person who is legally responsible for causing such injury." G.L. c. 231, § 85X.

a result of Samantha's illness than they have been. Despite being employed at the time, Lisa stayed at the hospital with Samantha throughout her six-month hospitalization; Rick did so as well. Both slept at the hospital every night, and each testified to the distress caused by the pain Samantha endured and by her devastating prognosis. During this time, they suffered many "close calls" when it appeared that Samantha would not survive. In the years that followed, both parents devoted their time to caring for Samantha's myriad needs, including feeding her through a tube for two years. A chef by trade, Richard has since taken employment at a local gasoline station because the shorter hours allow him to attend to Samantha's medical problems. He lamented at trial that due to Samantha's injuries and ongoing medical treatment, he is unable to see her enjoy a normal life. Cf. *Norman,* 403 Mass. at 315, 529 N.E.2d 139 (Liacos, J., dissenting) (one's child is valued because he or she "is a source of emotional sustenance and joy").

Based on the evidence before them, the jury could reasonably infer that Samantha would remain dependent upon her parents, "physically, emotionally, and financially," for the indefinite future. *Monahan,* 408 Mass. at 389, 558 N.E.2d 951. We recognize that the awards to Lisa and Richard are generous, but the evidence warrants the jury's finding that their lives have been "significantly restructured" in a manner justifying these awards.[49] See *id.* See also *Smith v. Kmart Corp.,* 177 F.3d 19, 30 (1st Cir. 1999), quoting *Wagenmann v. Adams,* 829 F.2d 196, 215 (1st Cir. 1987) ("Translating legal damage into money damages is a matter 'peculiarly within a jury's ken' ...").

Judgment affirmed.

IN THE SUPREME JUDICIAL COURT FOR THE COMMONWEALTH OF MASSACHUSETTS

John Adams Courthouse

One Pemberton Square
Suite 1400
Boston, Massachusetts 02108-1724

Telephone: 617-557-1020
Fax 617-557-1145

Nelson G. Apjohn, Esquire
Nutter, McLennen & Fish, LLP
World Trade Center West
155 Seaport Boulevard
Boston, MA 02210-2604
RE: No. SJC-11677

LISA RECKIS & OTHERS

V.

JOHNSON & JOHNSON & ANOTHER

NOTICE OF DENIAL OF PETITION FOR REHEARING

The Petition for Rehearing filed in the above captioned case has been considered by the Court and is denied.

Francis V. Kenneally, Clerk

Dated: June 10, 2015

To: Brandly M. Henry, Esquire

Nelson G. Apjohn, Esquire
Joan A. Lukey, Esquire
Plymouth Superior Court
Paul William Schhmidt, Esquire
Anthony Tarricone, Esquire
David R. Geirger, Esqurie
Martin W. Healy, Esquire
Charles Thomas Alagero, Esquire
Charlotte E. Glinka, Esquire
Elizabeth N. Mulvey, Esquire
Thomas R. Murphy, Esquire
Jeffrey S. Beeler, Esquire
Eric M. Gold, A.A.G.

COMMONWEALTH OF MASSACHUSETTS

COUNTY OF PLYMOUTH

THE SUPERIOR COURT

CIVIL DOCKET #PLVC2007-00064-A

LISA RECKIS AND RICHARD RECKIS, INDIVIDUALLY AND AS PARENTS AND NATURAL GUARDIANS OF THEIR MINOR CHILD, SAMANTHA T. RECKIS

Plaintiffs

vs.

JOHNSON & JOHNSON AND MCNEIL-PPC, INC. doing business as MCNEIL CONSUMER & SPECIALITY PHARMACEUTICALS

Defendants

VERDICT FORM

Negligence

1. Was the defendant, McNeil-PPC, Inc., negligent in failing to provide adequate warnings in connection with Children's Motrin?

Yes ✓ No _____

2. If the answer to Question 1 is "Yes," was the negligence a cause of harm to the plaintiffs?

Yes ✓ No _____

3. Was the defendant, Johnson & Johnson, negligent in failing to provide adequate warnings in connection with Children's Motrin?

Yes ✓ No _____

4. If the answer to Question 3 is "Yes," was the negligence a cause of harm to the plaintiffs?

Yes ✓ No _____

5. Did Samantha Reckis's ingestion of Children's Motrin cause her to develop Toxic Epidermal Necrolysis (TEN) in November of 2003?

Yes ✓ No _____

If the answer to Question 5 is "Yes," go to Question 6. If the answer to Question 5 is "No," you have reached a verdict.

Breach of Warranty

6. In November of 2003, was Children's Motrin defective in connection with the warnings provided by defendant McNeil-PPC rendering Children's Motrin unreasonably dangerous?

Yes ✓ No _____

7. If the answer to Question 6 is "Yes," was the defective warning a cause of harm to the plaintiffs?

Yes ✓ No _____

8. In November of 2003, was Children's Motrin defective in connection with the warnings provided by defendant Johnson & Johnson rendering Children's Motrin unreasonably dangerous?

Yes ✓ No _____

9. If the answer to Question 8 is "Yes," was the defective warning a cause of harm to the plaintiffs?

Yes ✓ No _____

Damages and Loss of Consortium

10. What amount of money will fairly compensate Samantha Reckis for all of her injuries and damages?

Fifty million dollars
(AMOUNT IN WORDS)

$50,000,000.00
(AMOUNT IN NUMBERS)

11. Did Lisa Reckis suffer a loss of her daughter's consortium (loss of society and companionship) as a result of the injuries suffered by Samantha Reckis?

Yes ✓ No _____

12. If you answered "Yes" to Question 11, what total amount of money will fairly compensate Lisa Reckis for her loss of consortium?

Six million five hundred thousand dollars
(AMOUNT IN WORDS)

$6,500,000.00
(AMOUNT IN NUMBERS)

13. Did Richard Reckis suffer a loss of his daughter's consortium (loss of society and companionship) as a result of the injuries suffered by Samantha Reckis?

Yes ✓ No _____

14. If you answered "Yes" to Question 13, what total amount of money will fairly compensate Richard Reckis for his loss of consortium?

Six million five hundred thousand dollars
(AMOUNT IN WORDS)

$6,500,000.00
(AMOUNT IN NUMBERS)

I certify that the answer to each question answered above was agreed to by at least ten out of twelve of the deliberating jurors.

Signature (signed)
Foreperson

Date: 2/13/13

COMMONWEALTH OF MASSACHUSETTS
COUNTY OF PLYMOUTH
THE SUPERIOR COURT

CIVIL DOCKET #PLVC2007-00064

LISA RECKIS AND RICHARD RECKIS, INDIVIDUALLY AND AS PARENTS AND NATURAL GUARDIANS OF THEIR MINOR CHILD, SAMANTHA T. RECKIS,

Plaintiffs,

vs.

JOHNSON & JOHNSON AND MCNEIL-PPC, INC. D/B/A MCNEIL CONSUMER & SPECIALITY PHARMACEUTICALS,

Defendants.

JUDGMENT

This action came on for trial before the Court and a jury, Christopher J. Muse, Justice, presiding, the issues having been duly tried and the jury having rendered its verdict, further, this action came on for trial without jury before the Court, Christopher J. Muse, Justice, presiding, upon the plaintiffs' cause of action for violation of Mass, Gen. Laws chapter 93A, the issues having been tried and the Court having issued its Findings of Fact, Rulings of Law and Order for Judgment, therefore,

It is **ORDERED and ADJUDGED:**

I. That the plaintiff, **Lisa Reckis and Richard Reckis as Parents and Natural Guardians of Samantha T, Reckis,** recover of the defendants, **Johnson & Johnson and McNeil-PPC, Inc., d/b/a McNeil Consumer & Specialty Pharmaceuticals** the sum of **$50,000,000.00** with interest thereon from November 28, 2006 to July 3, 2013 in the sum of **$39,600,346.50** as provided by law, and their costs of action.

II. That the plaintiff, **Lisa Reckis,** recover of the defendants, **Johnson & Johnson and McNeil-PPC, Inc., d/b/a McNeil Consumer & Specialty Pharmaceuticals** the sum of **$6,500,000.00** with interest thereon from November 28, 2006 to July 3, 2013 in the sum of **$5,148,045.05** as provided by law.

III. That the plaintiff, **Richard Reckis,** recover of the defendants, **Johnson & Johnson and McNeil-PPC, Inc., d/b/a McNeil Consumer & Specialty Pharmaceuticals** the sum of **$6,500,000.00** with interest thereon from November 28, 2006 to July 3, 2013 in the sum of **$5,148,045.05** as provided by law.

IV. That Count IV (Mass. Gen. Laws c. 93A) of the complaint of the plaintiffs, Lisa Reckis and Richard Reckis, Individually and as Parents and Natural Guardians of their minor child, Samantha T. Reckis, be and hereby is **DISMISSED.**

Dated at Plymouth, Massachusetts this 3rd day of July, 2013.

BY: (signed)
Assistant Clerk

Entered:
Copies mailed and emailed:

COMMONWEALTH OF MASSACHUSETTS

COUNTY OF PLYMOUTH, SS.

IN THE SUPERIOR COURT
C.A. No. 07-00064

LISA RECKIS AND RICHARD RECKIS,

INDIVIDUALLY AND AS PARENTS AND NATURAL GUARDIANS OF THEIR MINOR CHILD, SAMANTHA T. RECKIS,

v.

JOHNSON & JOHNSON, AND MCNEIL-PPC, INC, D/B/A/ MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

MEMORANDUM OF DECISION ON DEFENDANTS' MOTION FOR A NEW TRIAL

Defendants filed this this motion based on the following claims: The plaintiffs' theory of inadequate warning is preempted by federal law. The instructions that the Court gave to the jury were incorrect or incomplete statements of law. The special verdict form did not adequately reflect all of the key issues that the jury needed to decide. Plaintiffs' expert Dr. Randall Tackett gave opinion testimony that was either improper or outside of his qualifications. During plaintiffs' closing argument, counsel improperly appealed to the jury's sympathy for his client and bias against defendants. Plaintiffs presented excessively cumulative evidence on

contentious and material issues, which was unduly prejudicial to the defendants. The verdict was against the weight of the evidence. The evidence did not support the jury's unreasonably excessive award. And lastly, the jury calculated the compensatory damages using an averaging method, resulting in an impermissible "quotient verdict."

Most of the issues raised by the defendants in their pending Motion for New Trial were previously well presented and argued by the parties, thoroughly considered by the court, and hopefully, fairly reasoned and ruled upon by this Judge.[1] Briefly, but to the point, defendants have not presented any reason for the court to overrule or otherwise vacate any of its previous rulings. Nevertheless, as the court has already reviewed these voluminous pleadings, it will consider each of the claims in the order presented.

Defendants assert that this case was preempted by federal law. This issue was thoroughly briefed, and cogently argued, and guided principally by the holding in *Wyeth* v. *Levine, 555 U.S.555, (2008),* the court ruled that plaintiffs' failure to warn case was properly in the state court. There is no reason to disturb that ruling.

The court and the attorneys engaged in a substantial and somewhat collaborative charge conference. The collective goal was to provide the

---

[1] In addition to the five weeks of trial, the court held several days of pre-trial hearings, engaged counsel in an extensive charge conference, and issued memoranda on the parties post-verdict motions and oppositions.

jury with a clear and lucid expression of the law to guide them through the daunting task that confronts all jurors in the discharge of their oath, and particularly in this lengthy and somewhat complex case. The parties reached common ground on the majority of their proposed questions, and the court ruled on their disputed ones, prior to charge, and upon their objections at the conclusion of it. The court has reviewed those instructions, considered defendants' renewed objections to them, and finds that the instructions were complete, and correct.

Considerable time was spent by the parties and the court to draft special questions to direct the jury to its verdict. There was some disagreement between the parties, which the court refereed. The court has reviewed the defendants proposed questions, the final verdict form, and after consideration of the defendants' arguments, finds that the verdict form did reflect all the key issues required by the court's instructions.

The court entertained many trial objections related to the testimony of the plaintiffs' expert, Randall Tackett. His testimony was properly admitted. Notwithstanding the court's ruling on those objections, the jury was charged with a credibility instruction wherein they determined whether to believe any, some or all of the expert's testimony, with consideration of claimed expertise and underlying facts.

Defendants previously raised the issue of improper closing argument in their Motion for

Remittitur. At footnote 11 of the decision on that motion the court wrote:

The defendants argue that certain aspects of the plaintiffs' attorney's closing argument were improper and invited an excessive damage award. Nonetheless, the defendants never objected to the plaintiffs' attorney's closing argument during the trial, and this court never felt that it should have interrupted the plaintiffs' attorney's closing argument, sua sponte, for any reason. Hence, the plaintiffs' closing argument does not provide this court with a reason to order a remittitur.

For the same reason, this claim does not provide support for a new trial.

Throughout the trial, the court considered evidentiary objections by all parties, in the exercise of its most "mechanical" function. The court considered matters of relevance under sections 401 - 403 of the Massachusetts Guide To Evidence, including both the cumulative effect and possible unfair prejudice that might exist with otherwise relevant evidence, and made its ruling, sometimes with the benefit of argument by counsel. Upon reflection, the court declines to overrule itself.

The court timely ruled on defendants' Motions for Directed verdict at each juncture in the trial. It has also ruled on its concurrently filed Motion for Judgment NOV. As the trial and post verdict motions have been denied, and upon further consideration, the court finds this claim cannot provide a basis for a new trial.

The defendants, filed a detailed post-verdict Motion for Remittitur which addressed the claim that the jury's award was excessive. The court concluded:

Throughout the trial, the jury heard hours of testimony about Samantha's injuries and the pain and suffering she experienced as a result of the TEN. Translating Samantha's myriad of injuries into monetary damages was the jury's task, and their final monetary damage award was thoroughly supported by the record.

In addition, this court declines to disturb the jury's determination that $6.5 million would fairly compensate Lisa Reckis for her loss of consortium, and that $6.5 million would fairly compensate Richard Reckis for his loss of consortium. This court instructed the jurors that they could award Lisa Reckis and Richard Reckis damages for loss of society and companionship that they have suffered as a result of the defendants' negligence. They were to consider loss of comfort, solace, or moral support, any restrictions on social or recreational life, and any deprivation of the full enjoyment of the parent-child relationship. However, this court noted that there is no special formula or rule to measure a fair amount for loss of consortium and that the jurors were to use their own common sense, good judgment, experience, and conscience in awarding damages for loss of consortium. The evidence at trial established that since November of 2003, Lisa Reckis and Richard Reckis have devoted almost all of their attention to caring for Samantha-fmancially, emotionally, and

medically. TEN robbed the Reckises of their chance at enjoying a normal parent-child relationship with their daughter. Under the facts of this case, the jury's decision to award Lisa Reckis and Richard Reckis a total of $13 million for their loss of consortium was reasonable and supported by the evidence at trial. There is no reason to disturb this earlier ruling.

Lastly, the defendants again assert that the jury relied on an improper "Quotient Verdict." The court noted in its denial of defendants' Motion to Conduct Jury Voir Dire the following:

Under the circumstances presented by the unique facts of this case, this court is precluded from conducting a voir dire of the jury and probing into the jury's deliberations because there is no allegation before this court of any "extraneous prejudicial information" that was improperly brought to the jury's attention or any "outside influence" that was "improperly brought to bear upon any juror." See Mass. G. Evid. § 606(b) (2013). Accordingly, the defendants are precluded from attacking the purported quotient verdict through an individual voir dire of the jurors. See Tanner v. United States, 483 U.S. 107, 116-128 (1987) (recognizing that under proposed draft versions of Fed. R. Evid. 606(b) legislators noted that "a quotient verdict could not be attacked through the testimony of a juror"). Moreover, this judge is compelled to note that he observed this jury individually and collectively, gave their attention and interest to the evidence and to the court's rulings and instructions, through the long

and complicated trial. Each party was represented by excellent trial counsel, and consequently they lucidly educated and informed the jury about the issues in dispute, and the relevance of the evidence they each submitted in support of their respective claims and defenses. Their deliberations spanned fourteen hours, and they did nothing to warrant any finding except that they gave fair consideration to the evidence, and returned a verdict that was fair and just.

Individually and collectively, defendants claims do not provide a basis for a new trial. Their Motion is accordingly **DENIED.**

ORDER

Based on the foregoing, Defendants' Motion for New Trial is **DENIED**.

(signed)

September 6, 2013 Christopher J. Muse
Associate Justice

Entered copies mailed 9-17-13

COMMONWEALTH OF MASSACHUSETTS

COUNTY OF PLYMOUTH, SS.

IN THE SUPERIOR COURT
C.A. No. 07-00064

LISA RECKIS AND RICHARD RECKIS,

INDIVIDUALLY AND AS PARENTS AND NATURAL GUARDIANS OF THEIR MINOR CHILD, SAMANTHA T. RECKIS,

Plaintiffs,

v.

JOHNSON & JOHNSON, AND MCNEIL-PPC, INC, D/B/A/ MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

Defendants.

MEMORANDUM OF DECISION ON DEFENDANT'S MOTION FOR JUDGMENT NOTWITHSTANDING THE VERDICT

Defendants challenge the verdict in this case based on the following stated grounds:

1. Plaintiffs failed to prove their core contention that a different warning would have prevented Samantha Reckis from developing TEN. Further, the testimony offered by Plaintiffs could not support their claims as a matter of law because any claim

based on the subject warnings is preempted by federal law.

2. Plaintiffs did not produce evidence establishing the relevant standard of care for a reasonably prudent drug manufacturer or evidence that McNeil breached that standard.

3. Plaintiffs' claims fail because McNeil had no duty to warn of what Plaintiffs' own experts believe is an exceedingly rare and remote risk of developing TEN.

4. Plaintiffs' claims, which are expressly premised on their contention that McNeil withheld important safety information from the FDA, are preempted under *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001).

5. Plaintiffs failed to produce evidence sufficient to support a jury finding that Children's Motrin can cause TEN or that it caused Samantha Reckis to develop TEN.

6. Having abandoned an agency or alter ego theory of liability against Johnson & Johnson, Plaintiffs failed to adduce evidence to support a finding that Johnson & Johnson was liable to them as a direct tortfeasor because the uncontroverted evidence was that Johnson & Johnson never manufactured, distributed, marketed, or sold Children's Motrin.

Upon review of all the pleadings and consideration of applicable law, the court finds that there was sufficient evidence presented at trial to support the jury's verdict on each claim of

negligence, breach of warranty and loss of consortium. Defendants' Motion for Judgment Notwithstanding the Verdict is therefore **DENIED.**

September 6, 2013 (signed)

Christopher J. Muse
Associate Justice

Entered & copies mailed 9-17-13

COMMONWEALTH OF MASSACHUSETTS

COUNTY OF PLYMOUTH, SS.

IN THE SUPERIOR COURT
Civil Docket No. PLCV2007-00064B

RE: RECKIS, ppa et al

v.

JOHNSON & JOHNSON, et al

TO: Kaaty Meszaros, Esquire
Nutter McClennen & Fish

World Trade Center West
155 Seaport Boulevard
Boston, MA 02110

CLERK'S NOTICE

This is to notify you that in the above referenced case the Court's action on 09/17/2013:

RE: Defendants Johnson & Johnson and McNeil-PPC INC's MOTION to Alter or Amend judgment regarding application of interest, Pltffs' Memorandum in opposition

is as follows:

Motion (P#176) Denied for reasons previously set forth in in paper #161 (emergency motion) (Christopher J. Muse, Justice) dated 9/6/13. Entered and Notice sent 9/17/13

Dated at Plymouth, Massachusetts this 17th day of September, 2013.

Robert S. Creedon, Jr.
Clerk of the Courts

BY:

Adam Baker
Assistant Clerk
Telephone: (508) 747-8565
Copies mailed 09/17/2013

Pages: 224
Volume: V

COMMONWEALTH OF MASSACHUSETTS

PLYMOUTH s.s SUPERIOR COURT
DEPARTMENT OF THE
TRIAL COURT
Civil Action No. 2007-064

****

LISA RECKIS & RICHARD RECKIS *
Individually & as Parents & *
Natural Guardians of Their *
Minor Child, SAMANTHA RECKIS, *
Plaintiffs, *
vs. *
*
JOHNSON & JOHNSON, McNEIL-PPC, *
INC., d/b/a/ McNEIL CONSUMER & *
SPECIALTY PHARMACEUTICALS & *
JORDAN HOSPITAL, *
Defendants. *

****

Jury Trial
January 14, 2013
The Honorable Christopher J. Muse

At:
Plymouth Superior Court
52 Obery Street
Plymouth, Massachusetts

Ann Marie McDonald
Official Court reporter
Plymouth Superior Court
(508) 747-8586
***

THE COURT: You can all sit down. There is the outstanding motion that I told you about that is relating to the question of federal preemption. I am going to indicate as I did during the summary judgment, I know that that is not dispositive, but I am going to deny the Defendant's motion. I appreciate the reasoning of the Robinson case, but I differ with their conclusion.

As I see it and I asked my court reporter to give me a very clear view of as how the Defendant saw the issue, and she reported that the issue is: "Is there clear evidence that the FDA has already decided the question, and that is where the federal preemption comes, and that is what prevents the state jury from imposing liability for the lack of those two terms on the OTC label." I thought it was a well stated position. I asked Ann Marie to just copy it down, and I am resolving the issue against the Defendants and for the Plaintiffs, that evidence of may come in. There may be discussions. There may be argument for the inferences that might reasonably be drawn from the presence or absence of the terms of the several diseases or conditions as well as the language that we have discussed so much already. I also believe that there is relevance, obviously. I don't think there is any dispute about that. I don't think a preemption happening should

control. I don't believe that there is clear evidence that the FDA would not have approved the language. I will concede the fact that there is very compelling evidence of both sides. I just don't think that the Defendants have met their burden as been described in the Wyeth case.

Also I think it's important because this seems to be an evolving doctrine, it seems to me that as a fact matter, the evidence will be very strong on both sides in terms of — well at least from the Defendants' point of view, certainly. They will have the right to be able to argue all the facts of the history of what the Citizens' Petition reply indicates as well as all of the reasonable inferences from it. So the Plaintiffs may have a very uphill battle in terms of being persuasive on that issue, and that is why you have to prepare well for it, but I am not going to preclude the evidence.

I think I have addressed hopefully all of the matters that are outstanding, so we have a clear shot at the trial tomorrow.

***

MEMORANDUM

DATE: April 6, 2005

FROM: John K. Jenkins, M.D.
Director, Office of New Drugs (OND)

and

Paul J. Seligman, M.D., M.P. H.
Director, Office of Pharmacoepidemiology and Statistical Science (OPaSS)

Steven Galson, M.D., M.P.H.
Acting Director, Center for Drug Evaluation and Research

TO: NDA files 20-998, 21-156, 21-341, 21-042

Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk

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Executive Summary

Following a thorough review of the available data we have reached the following conclusions regarding currently approved COX-2 selective and non-selective non-steroidal anti-inflammatory drugs

(NSAIDs)[1] and the risk of adverse cardiovascular (CV) events:[2]

> * The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
>
> * Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
>
> * Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

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[1] A list of the non-selective NSAIDs is available on http://www.fda.gov/cder/drug/infopage/cox2/default.htm.

[2] The degree of COX-2 selectivity for any given drug has not been definitively established, and there is considerable overlap in in-vitro COX-2 selectivity between agents that have been generally considered to be COX-2 selective (e.g., celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib) and older NSAIDs that have been considered to be non-selective (e.g., diclofenac, ibuprofen, naproxen). For purposes of simplicity of discussion and comparisons, this document maintains the traditional separation between COX-2 selective and non-selective agents, but our use of this nomenclature should not be considered as FDA endorsement of such designations.

* Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

* Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).

* Controlled clinical trial data are not available to rigorously evaluate whether certain patients derive greater relief of pain and inflammation from specific NSAIDs compared to others or after failing to respond to other NSAIDs.

* The three approved COX-2 selective drugs reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs. Only rofecoxib has been shown to reduce the risk of serious GI bleeding compared to a non-selective NSAID (naproxen) following chronic use. The overall benefit of COX-2 selective drugs in reducing the risk of serious GI bleeding remains uncertain, as does the comparative effectiveness of COX-2 selective NSAIDs and other strategies for reducing the risk of GI bleeding following chronic NSAID use (e.g.,

concomitant use of a non-selective NSAID and a proton pump inhibitor).

* Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over other NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

Based on these conclusions, we recommend the following regulatory actions to further improve the safe and effective use of these drugs by prescribers, patients, and consumers:

* The agency should ask Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market. In the event Pfizer does not agree to a voluntary withdrawal, the agency should initiate the formal withdrawal procedures; i.e., issuance of a Notice of Opportunity for Hearing (NOOH).

* The professional labeling for all prescription NSAIDs should be revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning should also include the well described NSAID class risk of serious, and often life-threatening, GI

bleeding, which is currently contained in a bolded warning.

* Pending the availability of additional data, the labeling for all prescription NSAIDs should include a contraindication for use in patients immediately post-operative from CABG surgery.

* A class NSAID Medication Guide should be developed to inform patients of the potential increased risk of serious adverse CV events and the risk of serious GI bleeding.

* The labeling for non-prescription NSAIDs should be revised to include more specific information about potential CV and GI risks and information to assist consumers in the safe use of these drugs.

* The boxed warning for Celebrex (celecoxib) should specifically reference the available data that demonstrate an increased risk of serious adverse CV events and other sections of the labeling should be revised to clearly reflect these data.

* The agency should carefully review any proposal from Merck for resumption of marketing of Vioxx (rofecoxib). We recommend that such a proposal be reviewed by the FDA Drug Safety Oversight Board and an advisory committee before a final decision is reached.

* The agency should request that all sponsors of non-selective NSAIDs conduct and submit

for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

* The agency should work closely with sponsors and other interested stakeholders (e.g., NIH) to encourage additional long-term controlled clinical trials of non-selective NSAIDs to further evaluate the potential for increased CV risk.

Background

Vioxx (rofecoxib) was voluntarily withdrawn from the market by Merck in September 2004 following the observation of an increased risk of serious adverse CV events compared to placebo in a long-term controlled clinical trial. Subsequent to that action, reports of additional data from controlled clinical trials became available for other COX-2 selective NSAIDs that also demonstrated an increased risk of serious adverse CV events compared to placebo. These new data prompted the agency to conduct a comprehensive review of the available data and to present the issue for review at a joint meeting of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees on February 16-18, 2005.

Following the joint meeting, CDER conducted a thorough internal review of the available data regarding cardiovascular (CV) safety issues for COX-2 selective and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs). This memorandum summarizes the major issues considered in that

review, our conclusions regarding the interpretation of the available data, and our recommendations for regulatory actions necessary to further improve the safe and effective use of these drugs by prescribers, patients, and consumers.

Participants in the CDER review included staff from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, the Division of Over-the-Counter Drug Products, the Offices of Drug Evaluation II and V, the Office of New Drugs, the Office of Drug Safety, the Office of Biostatistics, the Office of Pharmacoepidemiology and Statistical Science, the Office of Medical Policy, the Office of Regulatory Policy, and the Office of the Center Director. Materials reviewed included the regulatory histories and the NDA and postmarketing databases of the various NSAIDs, FDA and sponsor background documents prepared for the Advisory Committee meeting, all materials and data submitted by other stakeholders to the Advisory Committee meeting, presentations made at the Advisory Committee meeting, the discussions held by the Committee members during the meeting, and the specific votes and recommendations made by the joint Committee.

Summary of available data

The most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long-term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. We will briefly summarize the available data from the long-term

controlled clinical trials for the three approved and two investigational COX-2 selective agents. We will also briefly summarize the available data from long-term controlled clinical trials to assess the potential for increased CV risk for the non-selective NSAIDs. Finally, we will briefly summarize the available data from observational studies that have sought to assess the potential for increased CV risk for NSAIDs. We will focus our discussion on the combined endpoint of death from CV causes, myocardial infarction (MI), and stroke, as that is a widely accepted endpoint in assessing the benefits and risks of a drug for CV outcomes. It should be noted that the exact definitions and adjudication procedures for this combined endpoint vary to some degree across the trials discussed below.

Celecoxib

The strongest data in support of an increased risk of serious adverse CV events for celecoxib comes from the National Cancer Institute's Adenoma Prevention with Celecoxib (APC) trial in patients at risk for recurrent colon polyps. In the APC trial a 2-3 fold increased risk of adverse CV events was seen for celecoxib compared to placebo after a mean duration of treatment of 33 months. There was evidence of a dose response relationship, with a hazard ratio[3] of 2.5 for celecoxib 200 mg twice daily

[3] The hazard rate is a measure of risk per unit of time in an exposed cohort (e.g., the event rate per month). The hazard ratio is the ratio of the hazard rates from the treatment group relative to the control group, and is often used to represent the relative risk when the relative risk is constant over time.

and 3.4 for celecoxib 400 mg twice daily compared to placebo for the composite endpoint of death from CV causes, myocardial infarction (MI), or stroke.

The results from the APC trial were not replicated, however, in the nearly identical Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial. Based on preliminary, unpublished data presented by the PreSAP investigators at the AC meeting, the hazard ratio was 1.1 for celecoxib 400 mg once daily compared to placebo for the composite endpoint of death from CV causes, MI, or stroke. It is worth noting that the dosing interval differed between the APC trial (twice daily) and the PreSAP trial (once daily), although both trials included a total daily dose of celecoxib of 400 mg. It remains unclear what, if any, role this difference in dosing interval may have played in the disparate findings between the two trials.

Another long-term controlled clinical trial of celecoxib versus placebo, the National Institute of Aging's Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) in patients at risk for Alzheimer's disease, also does not appear to have shown an increased risk for celecoxib 200 mg twice daily compared to placebo for the composite endpoint of death, MI, or stroke. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed no increased relative risk for celecoxib compared to placebo.[4] Finally, there was a small

[4] Relative risk is defined as the cumulative risk in the treatment group (e.g., number of events per the number of individuals in this group)

one-year trial comparing celecoxib 200 mg twice daily to placebo in patients with Alzheimer's disease that did not demonstrate a significantly increased risk of serious adverse CV events, but did show a trend toward more CV events in the celecoxib treatment arm.

The only available data from a long-term comparison of celecoxib to non-selective NSAIDs come from the Celebrex Long-Term Arthritis Safety Study (CLASS) in which celecoxib 400 mg twice daily was compared to diclofenac and ibuprofen in approximately 8000 patients with osteoarthritis or rheumatoid arthritis. No differences were observed for serious adverse CV events between celecoxib and the two non-selective NSAID comparators in this trial.

The ADAPT trial also included naproxen as an active control and will provide an additional comparison of celecoxib to a non-selective NSAID when the final study results become available. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed that celecoxib was intermediate between placebo (lowest incidence) and naproxen (highest incidence) for the composite endpoint of death, MI, or stroke.

Rofecoxib

The strongest data from a long-term placebo-controlled trial for an increased risk of serious adverse CV events with rofecoxib come from the

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divided by the cumulative risk in the control group. The term relative risk is often used interchangeably with the hazard ratio.

Adenomatous Polyp Prevention on Vioxx (APPROVe) trial in which rofecoxib 25 mg once daily was compared to placebo for up to three years. A relative risk of approximately two was seen for rofecoxib compared to placebo for serious adverse CV events. It is noteworthy that the rofecoxib and placebo CV event curves in a Kaplan-Meier plot did not appear to begin to separate until after approximately 18 months of treatment. In contrast to the results seen in APPROVe, two long-term placebo-controlled trials in patients with early Alzheimer's disease, including up to four years of treatment in a small number of patients, did not show a significant difference in CV events between rofecoxib 25 mg once daily and placebo.

The only long-term controlled clinical trial comparison of rofecoxib to a non-selective NSAID comes from the Vioxx Gl Outcomes Research (VIGOR) trial in which rofecoxib 50 mg once daily was compared to naproxen for up to 12 months. In VIGOR, rofecoxib was associated with a hazard ratio of approximately two compared to naproxen based on the composite endpoint of death, MI, or stroke. In contrast to the findings in APPROVe, in VIGOR the Kaplan-Meier CV event curves for rofecoxib and naproxen began to separate after approximately two months of treatment.

Valdecoxib

No long-term controlled clinical trials have been conducted comparing valdecoxib to either placebo or non-selective NSAIDs. Data are available from two short-term placebo- controlled trials of early dosing

with intravenous parecoxib (a pro-drug for valdecoxib) followed by oral valdecoxib in patients immediately post-operative from coronary artery bypass graft (CABG) surgery. In both studies, valdecoxib was associated with an approximately two-fold increased risk of serious adverse CV events compared to placebo. In contrast, a short-term placebo-controlled trial of intravenous parecoxib followed by oral valdecoxib in patients undergoing various types of non-vascular general surgical procedures showed no differences for serious adverse CV events.

Investigational COX-2 Selective Agents

Data from long-term controlled clinical trials are also available for two investigational COX-2 selective agents (lumiracoxib and etoricoxib), and were presented at the AC meeting. These data are summarized here as they provide further insights regarding the issue of CV risk for COX-2 selective agents and the comparison of CV risks between COX-2 selective drugs and non-selective NSAIDs.

The Therapeutic COX-189 Arthritis Research and Gastrointestinal Event Trial (TARGET) compared lumiracoxib 400 mg once daily to naproxen and ibuprofen for one year in approximately 18,000 patients with osteoarthritis. TARGET was designed as two sub- studies and the planned primary analysis was to be the combined lumiracoxib groups compared to the combined naproxen and ibuprofen groups. The study design, however, did not clearly reflect this intent since randomization occurred at the sub-study level rather than across the entire

study. For reasons that are not entirely clear, but possibly related in part to the randomization schema, the event rates for serious adverse CV events in the lumiracoxib groups in the two sub-studies were very different, i.e., 1.1 events per 100 patient years in the naproxen sub-study versus 0.58 events per 100 patient years in the ibuprofen sub-study. The event rates for serious adverse CV events for naproxen and ibuprofen were very similar in the two sub-studies; i.e., 0.76 events per 100 patient years for naproxen and 0.74 events per 100 patient years for ibuprofen.

The pre-specified primary analysis of TARGET found no difference in serious adverse CV events between the combined lumiracoxib groups and the combined naproxen and ibuprofen groups. The validity of combining the two lumiracoxib groups for purposes of the primary analysis is debatable, however, given the study design and the very different lumiracoxib event rates in the two sub-studies. It is unfortunate that the study design did not call for randomization of treatment assignment across the entire study, which would have allowed for a much more powerful comparison of lumiracoxib to the two non-selective NSAIDs.

Given the study design, the data from TARGET have also been analyzed by sub-study. In the naproxen sub-study, a hazard ratio of 1.44 was observed for the comparison of lumiracoxib and naproxen for serious adverse CV events. In the ibuprofen sub-study, a hazard ratio of 0.79 was observed for the comparison of lumiracoxib and ibuprofen for serious adverse CV events. The

observed differences between lumiracoxib and the NSAID comparators were not statistically significantly different in either sub-study.

Depending on which analysis of the TARGET study one considers, the conclusions may be very different. The pre-specified primary analysis would suggest that lumiracoxib, a highly COX-2 selective agent, is indistinguishable from two non-selective agents with regard to the risk of serious adverse CV effects. The sub-study results, however, would suggest that lumiracoxib may be associated with a slightly increased CV risk compared to naproxen and a slightly decreased CV risk compared to ibuprofen. The cross sub-study comparison of naproxen and ibuprofen, however, would suggest no difference in CV risk for these nonselective NSAIDs. Overall, this study does not support a clear distinction between lumiracoxib and the non-selective NSAIDs.

The Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial (EDGE) compared etoricoxib 90 mg once daily versus diclofenac for up to 16 months in approximately 7100 patients with osteoarthritis. The relative risk for serious adverse CV events was 1.07 for the comparison of etoricoxib to diclofenac (not significantly different). EDGE, therefore, is another large controlled clinical trial that did not distinguish COX-2 selective and non-selective NSAIDs with regard to CV risk.

Non-selective NSAIDs

Long-term placebo- and active-controlled trials are generally not available for the non-selective

NSAIDs, with the exception of the studies noted above where certain non-selective NSAIDs were used as active controls in studies of COX-2 selective drugs.

Observational studies

Data are available from a number of published and unpublished observational studies to address the issue of increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs. These studies have utilized a variety of designs, methods, source databases, and comparison groups, and each study has been characterized by strengths and weaknesses. In most of the observational studies, the estimated relative risks of the COX-2 selective NSAIDs have ranged from 0.8 to 1.5, with many point estimates not achieving statistical significance. These data were presented and discussed in detail at the AC meeting and the committee members generally agreed that the observational data could not definitively address the question of a modestly increased CV risk for the COX-2 selective compared to the non-selective NSAIDs, with the possible exception of data on rofecoxib 50 mg.

Overall, the most consistent finding for increased CV risk was observed for rofecoxib 50 mg, where statistically significant relative risks of approximately 2 and 3 were seen in two studies. The signal for increased CV risk for the 25 mg rofecoxib dose, however, was smaller and did not consistently achieve statistical significance. The relative risks in the seven observational studies for celecoxib ranged from 0.4 to 1.2, with statistical significance observed

once for a lowered risk and once for a higher relative risk. The available data for the non-selective NSAIDs from the observational studies are limited, and no consistent signals were observed.

Analysis and Conclusions

As noted above, the most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long- term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. The data from these trials, however, are not consistent in demonstrating an increased risk of serious adverse CV effects for COX-2 selective drugs. Perfect replication of study results cannot be expected, and is not required to reach a valid scientific conclusion. However, the degree of inconsistency observed in the data from long-term controlled clinical trials has a considerable impact on our ability to reach valid conclusions about the absolute magnitude of increased risk and to make risk versus benefit determinations for particular doses of specific drugs.

The data from controlled clinical trial comparisons of COX-2 selective and non-selective NSAIDs do not clearly demonstrate an increased relative risk for the COX-2 selective drugs, despite the substantial size of these studies. Only VIGOR clearly indicates such a difference with CLASS and EDGE giving no suggestion of a difference and TARGET giving analysis- dependent results. These findings, and the absence of any long-term placebo- or active- controlled clinical trials for most of the

non-selective NSAIDs, make it difficult to conclude that the COX-2 selective drugs as a class have greater CV risks than non-selective NSAIDs. The data from the well-controlled observational trials also have not provided consistent assessments of risk when comparing COX-2 selective and non-selective NSAIDs. The point estimates of the relative risk comparisons from these data are mostly in a range where interpretation may be difficult and influenced by uncontrolled residual confounding or biases often inherent in the design and data limitations of these studies.

Despite the limitations of the available data, overall, there is evidence, principally from a small number of placebo-controlled trials, that the approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, valdecoxib) are associated with an increased risk of serious adverse CV events (e.g., MI, stroke, and death). It remains unclear, however, that it is the presence of, or the degree of, COX-2 selectivity that accounts for these observations, as some have hypothesized. As noted above, in various controlled clinical trials, COX-2 selective drugs have been indistinguishable from non-selective NSAIDs (i.e., ibuprofen, diclofenac) in studies of substantial size and duration. Further, although on theoretical grounds the addition of low-dose aspirin (a COX-1 inhibitor) to a COX-2 selective drug should resolve any increased CV risk caused by COX-2 selectivity, this effect has not in fact been observed in several studies in which such comparisons are possible. Taken together, these observations raise serious questions about the so called "COX-2 hypothesis,"

which suggests that COX-2 selectivity contributes to increased CV risk. It, therefore, remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug's potential for an increased risk of adverse CV events compared to drugs that are less COX-2 selective.

After carefully reviewing all the available data, we believe that the data are sufficient to support a conclusion that celecoxib, rofecoxib, and valdecoxib are associated with an increased risk of serious adverse CV events when compared to placebo. For celecoxib and rofecoxib these conclusions are primarily supported by the data from the APC and APPROVE trials, respectively. However, for celecoxib a nearly identical long-term placebo-controlled trial (the PreSAP trial) and a similarly sized placebo-controlled trial in patients at increased risk for Alzheimer's disease did not replicate these findings. For rofecoxib, other long-term placebo-controlled trials of equal or greater duration (the Alzheimer's treatment trials) did not replicate the APPROVe findings. There are no long-term placebo-controlled trial data for valdecoxib. It is difficult to know how to extrapolate the findings from the parecoxib/valdecoxib CABG trials to the chronic use situation given the significant physiologic and traumatic impact on the coronary vasculature during and following CABG surgery, and the systemic pro-inflammatory response resulting from heart-lung bypass. We believe, however, that it is reasonable from a public health perspective to assume that valdecoxib does not differ from the other COX-2 selective agents with regard to increased CV risk

with chronic use pending the availability of data from long-term controlled clinical trials that would indicate otherwise.

The long-term controlled clinical trial data comparing COX-2 selective agents (i.e., celecoxib, rofecoxib, lumiracoxib, etoricoxib) to non-selective NSAIDs are limited in number, but include several trials of very substantial size. They raise significant unresolved questions. First, rofecoxib 50 mg clearly appears to have an increased risk of serious adverse CV events compared to naproxen based on the data from the VIGOR trial.[5] The absence of a placebo arm in the VIGOR trial, however, precludes a determination of whether chronic use of naproxen might also confer an increased risk of serious adverse CV events, albeit at a lower rate than rofecoxib. The VIGOR trial also does not provide a comparison between lower doses of rofecoxib and naproxen. Other controlled clinical trial data have also suggested some increased risk of serious adverse CV events for COX-2 selective agents versus naproxen (i.e., lumiracoxib in the naproxen sub-study in TARGET and etoricoxib in the NDA database); however, these studies also leave unresolved the question of whether naproxen is itself associated with an increased CV risk. The ADAPT trial is the only long-term controlled clinical trial in which a COX-2 selective agent and naproxen have

[5] Rofecoxib 50 mg is not recommended for chronic use in the approved labeling for Vioxx. The higher dose of rofecoxib was used in the VIGOR trial to provide a "worst case" estimate of the risk of serious GI bleeding for rofecoxib in comparison to naproxen.

been compared to placebo. The preliminary data from the ADAPT trial, however, do not appear to follow the pattern of the other COX-2 selective versus naproxen trials, showing a trend toward a higher event rate on naproxen compared to celecoxib and placebo (see above). Further, the cross sub-study comparison of naproxen and ibuprofen in TARGET suggests no difference in CV risk between these two non-selective NSAIDs. Taken together these data provide some support for the conclusion that a difference exits in the risk of serious adverse CV events between COX-2 selective agents and naproxen, but they do not provide any assurance that naproxen itself confers no increased CV risk; i.e., we cannot consider naproxen to be equal to or better than placebo.

The comparisons of COX-2 selective agents to certain other non-selective NSAIDs also raise interesting, and in the end unresolved, questions regarding the relative risk of COX-2 selective drugs compared to non-selective NSAIDs, despite the very large size of some of the trials. Several long-term controlled clinical trial comparisons of COX-2 selective agents to diclofenac have failed to provide evidence that diclofenac has a lower risk of serious adverse CV events than COX-2 selective agents (e.g., versus celecoxib in CLASS, versus etoricoxib in the NDA database, versus etoricoxib in EDGE). Large, long-term controlled clinical trial comparisons of COX-2 selective agents to ibuprofen, an unequivocally nonselective agent, also have failed to suggest a clear separation with regard to the risk of serious adverse CV events (e.g., versus celecoxib in

CLASS, versus lumiracoxib in the ibuprofen sub-study in TARGET). While even these large studies cannot rule out a small true difference in CV risk between COX-2 selective agents and diclofenac and ibuprofen, they show no clear trend and are best interpreted as showing that the risk of serious adverse CV events between COX-2 selective agents and either diclofenac and ibuprofen are in fact very similar. The latter interpretation, taken together with the findings of an increased risk of serious adverse CV events from the long-term placebo-controlled clinical trials of COX-2 selective agents, would support a conclusion that at least some of the non-selective NSAIDs are also associated with an increased risk of serious adverse CV events.

The inability to reliably estimate the absolute magnitude of the increased risk of serious adverse CV events for individual COX-2 agents, combined with the inability to reliably draw conclusions about the risk of COX-2 agents compared to one another or to other NSAIDs, highlights the conundrum the Agency faces in making decisions on appropriate regulatory actions. There is an urgent public health need to make appropriate regulatory decisions because the adverse events at issue are serious and a very large number of patients use selective and non-selective NSAIDs to treat chronic pain and inflammation. At the same time, erroneous conclusions and inappropriate actions are themselves potentially harmful to the public health. Although the currently available data are not definitive, the Agency cannot await more definitive data, which

may take years to accumulate from studies that have not even begun, before taking action.

In summary, we conclude that the three approved COX-2 selective drugs are associated with an increased risk of serious adverse CV events, at least at some dose, with reasonably prolonged use. We do not believe, however, that the currently available data allow for a rank ordering of the approved COX-2 selective drugs with regard to CV risk. We also believe that it is not possible to conclude at this point that the COX-2 selective drugs confer an increased risk over non-selective NSAIDs in chronic use. Naproxen may be an exception, but the comparative data to COX-2 selective agents are not entirely consistent, we do not have adequate long-term placebo-controlled data to fully assess its potential CV risks, and the cross sub-study comparison to ibuprofen in TARGET does not suggest a lesser CV risk. For the vast majority of non-selective NSAIDs we do not have any data that allow comparisons with COX-2 selective agents for CV risk, and where data exist, primarily from very large studies, they do not consistently demonstrate that the COX-2 agents confer a greater risk. Finally, there are no data from long-term placebo-controlled trials for the non-selective NSAIDs (other than the preliminary data for naproxen from ADAPT) that are analogous to the data available for the COX-2 selective agents.

The absence of long-term controlled clinical trial data for the non-selective NSAIDs significantly limits our ability to assess whether these drugs may also increase the risk of serious adverse CV events.

The long marketing history of many of these drugs cannot be taken as evidence that they are not associated with an increased risk of serious adverse CV events since CV events occur fairly commonly in the general population and small increases in common adverse events are impossible to detect from spontaneous reporting systems. The adverse CV risk signal for the COX-2 selective drugs became apparent only from large, long-term controlled clinical trials and large retrospective cohort studies. Similar clinical trials are needed to assess the potential risks of the non-selective NSAIDs.

Given our inability to conclude, based on the available data, that the COX-2 selective agents confer an increased risk of serious adverse CV events compared to non-selective NSAIDs, we believe that it is reasonable to conclude that there is a "class effect" for increased CV risk for all NSAIDs pending the availability of data from long-term controlled clinical trials that more clearly delineate the true relationships. This interpretation of the available data will serve to promote public health by alerting physicians and patients to this class concern and will make it clear that simply switching from a COX-2 selective agent to a non-selective NSAID does not mean that the potential for increased risk of serious adverse CV events has been fully, or even partially, mitigated.

With a "class effect" of NSAIDs on CV risk as a baseline, other factors must be considered in determining the overall risk versus benefit profile for individual drugs within the class and what, if any,

regulatory actions are appropriate. Some of the factors that must be considered include any demonstrated benefit of a given drug over other drugs in the class (e.g., superiority claims, effectiveness in patients who have failed on other drugs) and any unique toxicities (or absence of a toxicity) of a given drug over other drugs in the class.

With regard to greater or special effectiveness, while it is widely believed that patients differ in their response to NSAIDs, there are no controlled clinical trial data (e.g., studies in non- responders to a particular NSAID) to support such conclusions. Nonetheless, despite the lack of rigorous evidence, this widely accepted belief is at least in part a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients may choose. In addition, as noted above, there is no basis for concluding that the risk of serious adverse CV events for some NSAIDs is worse than the risk for the others, which supports maintaining a range of options.

With regard to toxicities, the primary goal in developing COX-2 selective agents was to reduce the serious, and often life-threatening, risk of gastrointestinal (GI) bleeding associated with chronic use of all NSAIDs. To date, the only COX-2 selective agent that has demonstrated a reduced risk for serious GI bleeding is rofecoxib, but only in comparison to naproxen. All of the approved COX-2 selective agents have been shown to reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs, but the

clinical relevance of this finding as a predictor of serious GI bleeding has not been confirmed (e.g., no difference in serious GI bleeding was observed in CLASS). Improved GI tolerability of NSAIDs is an important issue from an individual patient and public health perspective and is, at least in part, a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients may choose. Besides the COX-2 selective NSAIDs, other strategies are available that may reduce the risk of GI bleeding with NSAIDs (e.g., combined use of a non-selective NSAID with misoprostol or a proton pump inhibitor), but data are currently lacking on how these strategies compare to the use of COX- 2 selective drugs. With the exception of the comparison of rofecoxib to naproxen, data are not available to confirm a reduced risk of serious GI bleeding for the COX-2 selective agents, though it is widely believed that these agents are better tolerated by many patients.

In addition to the risk of serious and potentially life-threatening GI bleeding, NSAIDs are also associated with other potentially serious adverse effects, including, but not limited to, fluid retention, edema, renal toxicity, hepatic enzyme elevation, and bronchospasm in patients with aspirin-sensitive asthma. Comparative data to differentiate NSAIDs from one another with regard to these adverse effects are generally not available or are inconclusive.

Boxed warnings are currently included in the approved labeling for two single ingredient NSAID

products.[6] Bextra (valdecoxib) has a boxed warning for serious and potentially life-threatening skin reactions (i.e., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). Toradol (ketorolac) has a boxed warning emphasizing that it is approved only for short-term (<5 days) use in patients with moderately severe acute pain that requires analgesia at the opioid level, usually in a post-operative setting. Toradol is the only NSAID indicated for treatment of pain available for parenteral use (i.e., IV or IM injection); it therefore provides an important therapeutic option for physicians and patients in settings where the patient cannot take analgesics by mouth.[7] This therapeutic advantage favors continued availability of Toradol, despite the need for a boxed warning about the potential for increased frequency of serious adverse reactions with long-term (>5 days) use. In contrast, there are no data to support a unique therapeutic benefit for Bextra over other available NSAIDs, which might offset the increased risk of serious and potentially life-threatening skin reactions. While other COX-2 selective and non-selective NSAIDs also have a risk for these rare, serious skin reactions, the reported rate for these serious side effects appears to be greater for Bextra than for other COX-2 agents.[8]

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[6] The package insert for Arthrotec, a combination of diclofenac and misoprostol, includes a boxed warning, but the warning relates to potential toxicities of misoprostol, not diclofenac.

[7] Indomethacin is also available as a parenteral formulation, but is only indicated for parenteral use for treatment of patent ductus arteriosus.

[8] The agency has recently received a Citizens Petition regarding the

To date, the agency has received 7 reports of deaths from serious skin reactions in patients following treatment with Bextra. The occurrence of these serious skin reactions in individual patients is unpredictable, occurring with and without a history of sulfa allergy (valdecoxib is a sulfonamide) and after both short- and long-term use, which makes attempts to manage this increased risk difficult.

Several non-selective NSAIDs are currently available to consumers without a prescription (e.g., ibuprofen, naproxen, ketoprofen). The non-prescription doses of these products are generally well below the maximum daily prescription doses for the same active ingredient and the duration of treatment without specific alternate instructions from a physician is limited to 10 to 14 days. The applicability of the increased risk of serious adverse CV events as described above from controlled clinical trials to low-dose, short-term use of these non-prescription products for the relief of acute pain is unclear, although any such risk is expected to be minimal. No signal for increased risk of serious adverse CV events has been detected in the short-

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risk of Stevens-Johnson syndrome with ibuprofen (February 15, 2005). Although the petition is currently under review, and the agency has not reached a decision on the requested actions, based on analyses of data obtained before the petition was submitted, the agency has determined that the labeling for non-prescription NSAIDs should be updated to warn of the potential for skin reactions. Accordingly, along with the changes to the label to address CV risks, the agency will ask manufacturers of non-prescription NSAIDs to make these changes. After we have completed our review of the petition, we may determine that additional labeling changes with regard to potential skin reactions are warranted. The risk for serious skin reactions is already included in the labeling for most prescription NSAIDs.

term controlled clinical trials that supported the approval of these agents for treatment of acute pain. While these studies were primarily designed to evaluate effectiveness, the absence of a signal of increased CV risk provides some reassurance of the safety of short-term use. Further, with the exception of the parecoxib/valdecoxib CABG studies, the increased risk of serious adverse CV events in the controlled clinical trials described above have only become apparent after months to years of treatment. The parecoxib/valdecoxib data also provide support for the safety of short-term use. The two short-term placebo-controlled CABG studies showed an increased risk of serious CV events, but, a short-term placebo-controlled trial in general surgery patients did not show an increased risk. These data may suggest that in the absence of a predisposing condition, such as recent CABG surgery, the CV risk of short-term use of NSAIDs is very small, if any, particularly at low doses and given the typically intermittent nature of use of nonprescription NSAIDs for relief of acute pain.

Aspirin is also an NSAID that is available and widely used without a prescription. However, aspirin has other unique pharmacologic properties, including irreversible inhibition of platelet function, that distinguish it from the rest of the NSAID class. Further, data from long-term controlled clinical trials have clearly demonstrated that aspirin significantly reduces the risk of serious adverse CV events in certain patient populations (e.g., patients with a history of a MI). Aspirin, therefore, is an exception to the apparent "class effect" of increased

risk for serious adverse CV events for NSAIDs described above. Data from large, long-term controlled clinical trials clearly showing no increased CV risk or a reduction in CV risk would be necessary before concluding that other NSAIDs are also exceptions to the class risk.

Recommendations

We summarize below our recommendations for appropriate regulatory actions for the NSAID class and select individual agents.

NSAIDs as a class

Boxed Warning and Contraindication

We recommend that the professional labeling (package insert) for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, be revised to include a boxed warning highlighting the potential increased risk of CV events. The boxed warning should also include the well described risks of serious, and often life-threatening GI bleeding. We believe that a boxed warning with regard to potential increased CV risk is an appropriate response to the currently available data and will serve to highlight to physicians and patients that they must carefully consider the risks and benefits of all NSAIDs, as well as other available options, before deciding on a treatment plan for relief of chronic pain and inflammation. If it is determined that chronic use of an NSAID is warranted for an individual patient, the boxed warning will help to emphasize the importance of using the lowest effective dose for the shortest duration possible along

with appropriate attention to reduction of other risk factors for cardiovascular disease. The language of the boxed warning should be standardized across the class, with the exception of those situations where specific data or other information is available for an individual drug. In those cases, the standardized class wording should be maintained and the drug specific information added, including the results of any large controlled clinical trials.

The recommendation for a boxed warning for potential increased risk of CV events is supported by the unanimous vote of the Advisory Committees (28 yes) on the question of whether the labeling for the non-selective NSAIDs should be modified to include the absence of long-term controlled clinical trial data to assess the potential CV effects of these drugs.[9] While the AC did not specifically vote on a boxed warning, many of the committee members commented that such a warning would be an appropriate response given the current data. The Advisory Committees also strongly supported boxed warnings for the individual COX-2 selective drugs for increased CV risk.

The recommendation that the boxed warning also include the well recognized serious, and often life-threatening, risk of GI bleeding associated with chronic use of NSAIDs is intended to further reinforce the existing bolded warning. The GI bleeding risk with NSAIDs is clearly consistent with

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[9] There were 32 voting members of the Advisory Committees, but 4 members had left the meeting by the time this question was discussed.

our current approach to the use of boxed warnings, and placing this information in a boxed warning will serve to further emphasize this serious risk and ensure that physicians and patients keep this risk in mind as they are considering options for chronic therapy of pain and inflammation.

We also recommend that the labeling for all NSAIDs include a contraindication for use in patients in the immediate post-operative setting following CABG surgery. Data are only available in this setting from valdecoxib, but we have concluded that this short-term increased CV risk should be extrapolated to long-term use of valdecoxib. It is logical to also extrapolate this finding to other NSAIDs, pending the availability of other data that would suggest otherwise given the serious nature of the adverse events noted in the valdecoxib CABG study and the high-risk nature of the patients undergoing CABG surgery. The contraindication for NSAID use in this setting would NOT apply, however, to aspirin for the reasons noted above.

Medication Guide

We recommend that the patient labeling for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, include a Medication Guide. The Medication Guide should focus on the potential increased risk of serious adverse CV events and the risks of serious GI bleeding. The Medication Guide will also inform patients of the need to discuss with their doctor the risks and benefits of using NSAIDs and the importance of using the lowest effective dose for the shortest duration possible if treatment with

an NSAID is warranted. To avoid confusion and to allow for more rapid implementation, we recommend that the text of the Medication Guide be standardized across the class, following the model that was recently successfully implemented for anti-depressants.

Comprehensive Data Review and New Studies

We recommend that the agency request that the sponsors of all non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of all available data from controlled clinical trials to further evaluate the potential risk of serious adverse CV events. The search and analysis strategy should be similar across sponsors and drugs. The agency should carefully review the data as they become available and take any appropriate regulatory actions based on the findings.

The agency should also work closely with sponsors of non-selective NSAIDs and other stakeholders (e.g., NIH, professional associations, patient groups) to encourage the conduct of additional long-term controlled clinical trials of the non-selective NSAIDs to better evaluate the potential for increased risk of serious adverse CV events.

Non-prescription NSAIDs

We recommend that the NSAIDs that are currently available without a prescription for the short-term treatment of acute pain continue to be available to consumers. While this would apparently represent the first time that products that have a

boxed warning in the prescription package insert would also be available for non-prescription use, we believe the available data support a conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious adverse CV events. The overall benefit versus risk profile for the non-prescription NSAIDs remains very favorable when they are used according to the labeled instructions, and we believe that it is important to maintain a range of therapeutic options for the short-term relief of pain in the OTC market. Further, the other available non-prescription drugs for short-term relief of pain and fever can also be associated with serious, and potentially life-threatening, adverse events in certain settings and patient populations.

To further encourage the safe use of the non-prescription NSAIDs, we believe that the labeling for these products should be revised to include more specific information about the potential CV and GI risks, instructions about which patients should seek the advice of a physician before using these drugs, and stronger reminders about limiting the dose and duration of treatment in accordance with the package instructions unless otherwise advised by a physician. In addition, as noted earlier, the agency has determined that the labeling for non-prescription NSAIDs should be revised to warn of the potential for skin reactions. We also recommend that the Agency continue its current consumer education efforts regarding the safe and effective use of non-prescription pain relievers and that this new information be highlighted in those campaigns.

CELEBREX®. NDA 20-998/NDA 21-156 (celecoxib capsules)

After carefully reviewing all the available data, we conclude that the benefits of celecoxib outweigh the potential risks in properly selected and informed patients. Therefore, we recommend that celecoxib remain available as a prescription drug with the revised labeling described below in addition to the NSAID class boxed warning, contraindication, and Medication Guide described above.

Boxed warning and other labeling changes

We recommend that the boxed warning for Celebrex include specific reference to the controlled clinical trial data that demonstrate an increased risk of serious adverse CV events (e.g., the APC trial). The text in the box may be brief and include a reference to the CLINICAL PHARMACOLOGY, Clinical Studies section of the labeling where the available long-term controlled clinical trial data should be described in greater detail.

Finally, we recommend that the INDICATIONS section of the labeling be revised to clearly encourage physicians to carefully weigh the potential benefits and risks of celecoxib and other treatment options for the condition to be treated before a decision is made to use Celebrex, and to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Postmarketing study commitment

We strongly recommend that CDER request a written commitment from the sponsor to conduct an

additional long-term study (or studies) to address the safety of celecoxib compared to naproxen and other appropriate active controls (e.g., other non-selective NSAIDs, appropriate non-NSAID active comparators). CDER should be actively involved in the design of the trial(s) and insist on aggressive timelines for initiation and completion of the study(ies).

The above recommendations are consistent with the votes and recommendations made by the Advisory Committees for Celebrex. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for celecoxib. After carefully considering all the available data, the Advisory Committees voted 31 yes to 1 no in response to the question: " Does the overall risk versus benefit profile of celecoxib support marketing in the US?" While specific votes were not taken on the issue of what labeling changes and other risk management options would be appropriate, the overwhelming majority of the Advisory Committee member voiced their support for a boxed warning, a Medication Guide, and postmarketing study commitments to further explore the long-term safety of Celebrex in comparison to other appropriate comparators.

BEXTRA®, NDA 21-341 (valdecoxib tablets)

After carefully considering all the available data and risk management options, we have concluded that the overall risk versus benefit profile for Bextra is unfavorable at this time. We therefore recommend that Bextra be withdrawn from the U.S. market. We

have concluded, as noted above, that Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in short-term CABG trials and that it is reasonable from a public heath perspective to extrapolate these findings to chronic use. The increased risk of serious adverse CV events alone, however, would not be sufficient to warrant withdrawal of Bextra since we have no data showing that Bextra is worse than other NSAIDs with regard to CV risk. Our recommendation for withdrawal is based on the fact that, in addition to this CV risk, valdecoxib already carries a boxed warning in the package insert for serious, and potentially life-threatening, skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) and FDA has received 7 spontaneous reports of deaths from these reactions. The reporting rate for these serious skin reactions appears to be greater for Bextra than other COX-2 selective agents. Further, the risk of these serious skin reactions in individual patients is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use, which makes risk management efforts difficult. To date, there have been no studies that demonstrate an advantage of valdecoxib over other NSAIDs that might offset the concern about these serious skin risks, such as studies that show a GI safety benefit, better efficacy compared to other products, or efficacy in a setting of patients who are refractory to treatment with other products.

The recommendation that Bextra be withdrawn is supported, at least in part, by the specific votes and

recommendations of the Advisory Committees. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for valdecoxib. In response to the question "Does the overall risk versus benefit profile of valdecoxib support marketing in the US?" the Advisory Committees voted 17 yes and 13 no with 2 abstentions. Several of the advisory committee members who voted no expressed concerns about the strong signal of CV risk from the CABG trials, the absence of long-term controlled trial data to more clearly define the potential CV risks of Bextra, the fact that Bextra already carried a boxed warning for serious skin reactions, and the fact that there were no data to support a conclusion that Bextra offered a therapeutic advantage over NSAIDs.

One potential argument in favor of continued marketing of valdecoxib is that it provides an additional therapeutic option for management of arthritis and that prescribers and patients could be informed of the potential increased risk of CV events and serious GI bleeding, in addition to the potential for serious and possibly life-threatening skin reactions, and be allowed to make individualized treatment decisions. This approach, in fact, was strongly favored by practicing rheumatologists on the Advisory Committee. It is important to note, however, that there are more than 20 other NSAIDs on the market. This range of options diminishes the value of continued marketing of valdecoxib, particularly in the face of an already existing boxed warning regarding serious, and potentially life-

threatening, skin reactions and the fact that there are no data that demonstrate that valdecoxib offers any therapeutic advantage over other NSAIDs.

We recommend that FDA request that Pfizer voluntarily withdraw Bextra from the U.S. market. If Pfizer does not agree to that request, we recommend that FDA initiate the formal withdrawal process by preparing and publishing a Notice of Opportunity for Hearing.

We recommend that FDA remain open to allowing limited access to valdecoxib under an IND to those patients who believe that it is their best option, if the sponsor proposes such an IND. If additional clinical trials subsequently demonstrate that valdecoxib does not have an increased CV risk (or if its risk is significantly less than other available agents) or a therapeutic advantage for valdecoxib over other NSAIDs, FDA should carefully consider those data and reassess the current conclusions regarding the overall risks and benefits for valdecoxib.

VIOXX ®. NDA 21-042 (rofecoxib tablets and oral suspension) VIOXX was voluntarily withdrawn from the U.S. market by the sponsor on September 30, 2004, following the announcement of the results from the APPROVe trial. Therefore, no regulatory action is warranted at this time. Should the sponsor seek to resume marketing for rofecoxib, a supplemental NDA with revised labeling will be required. The supplemental NDA would require FDA review and approval prior to implementation of the new labeling since the changes would not be of the type allowed under FDA regulations for a "Changes Being

Effected (CBE)" labeling supplement The supplemental application should specifically outline the sponsor's proposal for revised labeling designed to provide for safe and effective use of the drug in populations where the potential benefits of the drug may outweigh potential risks, and all data and arguments that support resumption of marketing.

We believe that FDA should carefully review any such proposal submitted by the sponsor. We would also recommend that the FDA Drug Safety Oversight Board (DSB) and an advisory committee be consulted before a final decision is taken. Our rationale for recommending review by the DSB and an advisory committee includes the following factors. First, there is limited precedent for a drug that has been withdrawn from the U.S. market for safety reasons to be returned to marketing. The only recent example that we can recall was Lotronex, and that application was reviewed by an advisory committee before FDA reached a final decision on the sponsor's request.[10] Second, concerns were expressed at the recent advisory committee meeting that Vioxx may be associated with a higher risk of increased blood pressure, fluid retention, and congestive heart failure than other COX-2 selective NSAIDs. We believe that these additional potential serious risks of Vioxx need to be fully explored through a public process before a decision is made regarding resumed marketing. Third, the recent advisory committee meeting was a general issues meeting, not one

[10] The FDA Drug Safety Oversight Board had not been established at the time of the review of the Lotronex resubmission.

specifically devoted to the issue of resumption of marketing of Vioxx. While the committees narrowly voted in the affirmative that the overall risk versus benefit profile of rofecoxib supported marketing in the U.S., the committee members expressed a wide variety of often contradictory opinions on what regulatory actions (e.g., labeling changes, risk management efforts) would be appropriate to allow resumed marketing. Specific votes were not taken on these important issues, and we believe the agency would benefit from the advice of an advisory committee meeting specifically devoted to the resumption of marketing of Vioxx before the FDA reaches a decision on final action. Finally, the withdrawal of Vioxx has been the subject of intense public interest and debate, and we believe that a transparent process for reaching an agency decision on resumption of marketing is needed to ensure public confidence in the agency's decision-making process.

February 15, 2005

Food and Drug Administration
Dockets Management Branch
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition to Request Risk Assessment of the Risks from SJS and TEN associated with ibuprofen; the Addition of Critical Safety Information relating to Serious Skin Reactions Associated with the Use of Ibuprofen to All Prescription and OTC Labeling; and Investigation into the withholding of critical safety information by McNeil Pharmaceuticals and Wyeth Consumer Healthcare.

Dear Sir/Madam,

Pursuant to 21 CFR 10.30, the enclosed Citizen Petition has been prepared to request that the FDA conduct a full risk assessment of the risks from SJS and TEN associated with ibuprofen, and an investigation into why McNeil Pharmaceuticals and Wyeth Consumer Healthcare withheld critical safety information from the FDA and the American public regarding the risks of SJS and TEN associated with ibuprofen. Remedies from that assessment should include the amplification of the current Ibuprofen prescription and either reconsider the OTC status of

the pediatric formulation or, at minimum, enhance OTC labeling to properly reflect the increased risk of Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with ibuprofen.

The current OTC labeling in the U.S. provides no information relating to the substantially increased risks of SJS and TEN associated with ibuprofen, and the prescription labeling in the U.S. fails to adequately and prominently describe the magnitude and severity of these adverse events. Neither label provides physicians or the patient information critical to reducing the risk of harm from SJS and TEN by identifying the early symptoms of SJS and TEN and to discontinue the medication at the first sign of a rash, unexplained or persistent fever, or any mucosal lesion. This instruction to physicians and patients is vital to reduce the risk and severity of SJS and TEN, and to prevent any further risks of morbidity and mortality associated with these exfoliating diseases.

Please contact the undersigned if you have any questions or require additional information.

Very truly yours,

(signed)

Roger E. Salisbury, M.D.
Professor of Surgery
Chief of Plastic Surgery
New York Medical College
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cc: Commission of Department of Health and Human Services
Assistant Secretary for Health
Acting Director, CDER (Desk Copy)
The Honorable U.S. Senator Christopher Dodd
The Honorable U.S. Senator Charles E. Grassley

THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

February 15,2005
Docket No. 2005P-0072

Citizen Petition to Request Risk Assessment of SJS and TEN; and Investigation of Withholding of Safety Information regarding Risks of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Ibuprofen products; and the Addition of Critical Safety Information Relating to Serious Skin Reactions Associated with the Use of Ibuprofen to All Prescription and OTC Labeling;

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CITIZEN PETITION

I. Introduction and Action Requested

Roger E. Salisbury, M.D., Michael "Rusty" Nicar, Ph.D., Randall Tackett, Ph.D., Steven Pliskow, M.D., Darlene and Andrew Kiss, and other parents of victims of SJS and TEN caused by ibuprofen products submit this petition to request action by the Food and Drug Administration (FDA) relating to the drug product, ibuprofen (Motrin, Advil, etc.). Further, petitioners are requesting that a full risk assessment of SJS and TEN associated with ibuprofen be conducted by the FDA. Petitioners are further seeking the FDA to conduct an investigation into the withholding of critical safety information

regarding the risks of SJS and TEN associated with ibuprofen by McNeil Pharmaceuticals, manufacturer of Motrin products, and Wyeth Consumer Healthcare, manufacturer of Advil products, both from the FDA and the American public. Additionally, the petitioners request that FDA require the manufacturers of ibuprofen to amplify their prescription and OTC labeling to adequately warn prescribers, health care professionals and consumers of the increased risk of Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) associated with ibuprofen that has been established in the scientific literature since 1978 through the present. Further, petitioners request that additional warnings and instructions be provided in the Warnings and Precautions section of any prescription labeling for all ibuprofen products sold in the U.S. to include a specific warning about the risk of serious skin reactions like SJS and TEN, and to disclose to physicians and consumers instructions to discontinue any/all ibuprofen product(s) at the first sign of a rash, mucosal blisters or sores in the mouth, eyes, throat, or genitalia, and any unexplained or persistent fever.

The proposed actions include the addition of a bolded Black Box Warning in the prescription labeling to comply with 21 CFR 201.57, and the dissemination of "Dear Doctor" and "Dear Healthcare Professional" letters to alert prescribers, pharmacists, medical associations, bum centers, and hospitals to this critically important information. The Petition also requests amplification of multiple sections of the OTC label for ibuprofen products,

including placement of critical information regarding the risks of SJS and TEN associated with ibuprofen in the "Warnings" and "Stop Use" sections on all ibuprofen products sold in the U.S. (21 CFR 201.66)

This Petition is submitted pursuant to 21 CFR 10.30, and relates to Sections 201(n), 502 (a), 502 (f)(1) and 505 of the Federal Food, Drug and Cosmetic Act; and 21 CFR 201.57 and 21 CFR 201.66.

II. Statement of Factual Grounds

A. The Current Ibuprofen Labeling Fails to Comply with FDA Labeling Requirements

The Federal Food, Drug and Cosmetic Act and the Code of Federal Regulations provide specific requirements for the content and format of labeling materials relating to prescription drug products. Pursuant to 21 CFR 201.57, the **Warnings** section must describe all serious adverse reactions and potential safety hazards, limitations in use imposed by them, and actions to be taken if these events should occur. Events leading to serious injury or death may be placed in the Warnings section in a prominently displayed box for added emphasis.

FDA regulations note that pharmaceutical product labeling must be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug. A causal relationship need not have been provided. In order to alert prescribers to new warnings as soon as possible, FDA also permits manufacturers to add

new warnings to their labeling without first securing FDA approval (21 CFR 314.70).

The current labeling for prescription ibuprofen products does not provide any information relating to SJS and TEN in the Warnings (or even the Precautions) section of the insert. These sections are required to include the most critical information relating to product safety and the steps to be taken to ensure safe product use. Obviously, these sections of the package insert for prescription ibuprofen products should describe the increased risk of SJS and TEN associated with ibuprofen that has been established in the scientific literature, and in conjunction with the rising numbers of serious skin reactions associated with ibuprofen use and precautionary procedures to halt progression of these events. Based on available literature and adverse event data, this information should have been added to the Warnings section of the labeling several years ago. Because toxic epidermal necrolysis has a 30% mortality rate and has been reported to be as high as 80% in certain populations, it is important to provide warnings and instructions in the prescription package inserts for ibuprofen products to alert the prescriber to these risks and steps to reduce the harm from these life-threatening and fatal reactions.

Other prescription package inserts have such warnings and precautions, even though their risks of SJS and TEN are lower than ibuprofen. For example, Zithromax (azithromycin) carries a SJS and TEN warning, but the scientific literature reports that it has a lower relative risk for SJS and TEN than

ibuprofen. Moreover, the FDA has approved a black box warning for the COX-II NSAID Bextra to specifically warn about the risk of SJS and TEN associated with Bextra, and we believe that the same warning should be placed on prescription ibuprofen products based on the scientific evidence that is available in the spontaneous adverse event databases and the scientific literature.

SJS and TEN are adverse events that are noted in the package insert for prescription ibuprofen products in the in the Adverse Reactions section. However, there is no discussion or information relating to the magnitude and severity of these events in the Warnings section, or any discussion about the increased risks of SJS 4 and TEN that as been established in the scientific literature, as well as the rise in case reports in the scientific evidence observed over the last several years. The precautions to be taken to halt the progression of early symptoms of SJS and TEN are also not specifically described in any ibuprofen labeling, whether prescription or OTC.

FDA laws and regulations also specify the format and content of OTC product labeling pursuant to 21 CFR 201.66. Because medical intervention does not usually accompany OTC use, specific sections are available in OTC labeling to assist patients with recognition of potentially serious adverse events and to understand those situations in which drug use should be stopped and medical attention should be sought.

Unfortunately, the current U.S. OTC labeling for ibuprofen products does not provide any description or information relating to EM, SJS, or TEN. As such, patients are not alerted to the severity of these skin reactions and are not instructed to discontinue all ibuprofen use if/when any of the early symptoms of SJS and TEN occur.

Ibuprofen manufacturers cannot reasonably argue that the current Allergy Alert in the OTC label is in any way related to SJS and TEN. A review of the New Drug Applications submitted by these manufacturers confirms that the FDA considered the allergy alert to be intended for anaphylaxis related events which occur in aspirin sensitive patients. The allergy alert statements on the ibuprofen 5 labeling are not directed to SJS/TEN events. However, if aspirin sensitivity is deemed to necessitate a Warning statement, then the ibuprofen-related SJS/TEN events certainly warrant similar labeling attention. After all, there are significantly more skin-related events than allergic reactions associated with ibuprofen use.

Both the prescription and OTC labels employed in the U.S. fail to comply with the labeling requirements needed to ensure patient safety. Paragraph C provides an analysis of the international labeling employed with ibuprofen products. It will be seen that U.S. prescribers and patients are provided with substantially less information relating to SJS and TEN than patients receiving ibuprofen outside the United States. Furthermore, to our knowledge, McNeil

Pharmaceuticals and Wyeth Consumer Healthcare have not filed this foreign labeling with the FDA in their Annual reports for their respective pediatric ibuprofen products to alert the FDA that they employ different labeling in foreign countries.

B. The Medical and Scientific Literature Confirm Causal Relationship between SJS and TEN associated with Ibuprofen, as well as increasing risks of Serious Skin Reactions Associated with Ibuprofen Use.

Ibuprofen is an effective drug that is generally well tolerated in adults and children. It is effective for pain and inflammation in adults and for fever in children. FDA has rejected the applications for the pain indication for pediatric ibuprofen suspension submitted by McNeil and Wyeth in the past. However, using a new federal regulation instituted in 1994, both applications were approved by the 6 Agency based on extrapolation of data from adult studies of ibuprofen, and the pediatric formulation of ibuprofen was approved for prescription and OTC use for pain and fever. Under the supervision of a physician, the use of ibuprofen in treating fever should be reserved for those children with high or long-lasting fever. Under a physician's care, early signs of severe morbidity (eg., renal failure, toxic skin reactions) could be monitored for, and when they occur, the drug could be rapidly withdrawn and treatment commenced. OTC status for treatment of common fever in children, especially otherwise healthy children, affords a different benefit-risk balance. This benefit-risk would be quite favorable,

even given the discretionary nature of mild - moderate fever pharmacotherapy, if it were not for two rare, but very severe adverse drug reactions, SJS and TEN.

Based on the review of NDAs, scientific literature and other relevant materials, we believe that substantial evidence for the causal relationship between ibuprofen and SJS and TEN existed when the first prescription pediatric formulations Pediaprofen and Children's Advil were approved in 1989. Substantial confirmation of that causal relationship has continued to accumulate over the ensuing years both in the scientific literature and in pharmacoepidemiology studies.

The casual relationship between NSAIDS and rare but severe skin reactions (SJS, TEN) is well-documented and recognized by the leaders of the dermatology community. Though the reactions rates are suspected to vary by sub-type of 7 NSAID, all have been implicated, including ibuprofen. Those facts have already been recognized by the FDA, McNeil and Wyeth so that the product labeling for prescription Children's Motrin and Children's Advil contains the following:

Incidence less than 1% (Probable causal relationship) "Skin and appendages " Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson's Syndrome, alopecia, exfoliative dermatitis, Lyell 's syndrome (toxic epidermal necrolysis), photosensitivity reactions.

Evidence in support of this causal relationship between ibuprofen and SJS and TEN are from

clinical case reports that have been reported since the late 70's until present in adults and children. After 1995, substantial additional evidence of this relationship has been accumulated, much of it specific to ibuprofen. In addition to the case reports of ibuprofen induced SJS and TEN since 1995, the SCAR study group consisting of very well respected dermatologists and epidemiologists in the scientific community conducted a international case-control study that demonstrated a statistically significant causal relationship between ibuprofen and SJS and TEN with a RR of 5.3, 95% CI 1.2-25. (Mockenhaupt, et. al. 2003) McNeil and Wyeth sponsored studies such as the Boston University Fever Study (BUFS) and the Children's Analgesic Medicine Project (CAMP) which were used in support of their applications for the Rx. to OTC switch, which were 8 approved in 1995 and 1996, respectively. While these studies were informative about the common safety profile of ibuprofen in the pediatric population, they were uninformative toward the assessment of the risk for rare and severe reactions such as SJS or TEN. Despite the request from the FDA to the sponsors to design these postmarketing safety studies (BUFS & CAMP) to evaluate the rare, but serious adverse events associated with pediatric ibuprofen, we further believe that these issues were not adequately studied. Moreover, McNeil and Wyeth have failed to provide the FDA full information regarding the safety issues surrounding serious skin reactions, including SJS/TEN that were not presented in their applications for their OTC pediatric formulations.

Evidence of causal relationship and increased risks were in existence prior to OTC switch of the pediatric formulation in 1995-1996 and thru the present

There was considerable experience with ibuprofen beginning with its U.S. approval for arthritis in adults in 1974. It rapidly became the most widely prescribed NSAID. Its common safety profile was excellent. There was, however, developing evidence for a number of rare but severe adverse outcomes associated with its use. Most notably they are severe skin reactions and kidney failure. The cumulative evidence base on SJS and TEN are presented in Tables 1-5. Regulatory milestones are noted on the relevant tables.

It is clear that the labeling change in 1982 that added SJS as "probably related" was based on a substantial set of accumulated evidence. The addition of TEN as being "probably related" in 1994 was based on both a better understanding the SJS-TEN continuum and further accumulated evidence.

Table 1: Accumulation of Knowledge of Risk of SJS/TEN in Adults associated with NSAIDs (1978 thru 1989)

WHAT	WHEN"	HOW	How Strong	References
NSAIDS (Adults) & SJS/TEN	1983	Case reports of SJS/TEN	Suggestive (Signal)	FDA review (Judith Jones, 1983) - FDA-FOI, WHO, CSM - Skin ADEs (1974-1989) McNeil & Wyeth databases
NSAIDs (Adults) & SJS/TEN	1984-1987	Published case reports of	Supportive	(l)Stern R., et al., JAMA, Vol. 252, No. 11, pp. 1433-7, (1984);

		SJS/TEN in literature		(2) Stern R., et al., Jour of Amer Acad Derma, Vol. 12, No. 5, Part 1, pp. 866-75, (1985); (3)Stern, RS, et al., Current Perspectives in Immunodermatology, Chapter 6, pp. 75-97 (1984); (4) O'Brien, WM, et. al., J Rheumatology, 12: pp. 13-20 (1985) (5) Roujeau J., Scand J Rheumatology, Suppl. 65, pp. 131-4, (1987); (6) Roujeau J., et al., Arch Dermatol, Vol. 123, pp. 1166-70, (1987); (7) Stern R., et al., Arch Dermatol, pp. 3-17,(1987)
NSAIDs (Adults) & SJS/TEN	1989	Published or sponsored studies	Supportive	(1) Stem R., et al., J Am Academy of Dermatology, Vol. 21, No. 2, Part 1, pp. 317-22, (1989);(2)Bigby, M, et. al., Primary Care, Vol. 16, No. 3, pp. 713-727 (1989)
Ibuprofen (Adults) & SJS/TEN	1983	Case reports of SJS/TEN	Supportive	- McNeil and Wyeth internal reports (1983); -UK CSM Roster of Skin
				ADEs (1969-1983) -FDA-FOI, WHO, CSM - Skin ADEs (1974-1989) Wyeth databases
Ibuprofen (Adults) & SJS/TEN	1978-1989	Published case reports	Supportive	(1) Sternlieb P., et al., NY State Jour of Med. pp. 1239-43, (1978); (2) Stem R,, et al., JAMA, Vol. 252, No. 11, pp. 1433-7 (1984); (3) Stem R., et al..

				Jour of Amer Acad Derma. Vol. 12. No. 5. Part 1, pp. 866-76, (1985); (4) O'Brien, WM, et. al., J Rheumatoloev. 12: pp. 13-20 (1985); (5) Laing, et. al. J Am Acad Derm, 19: pp. 91-94 (1988).
"Probable Causal Relationship" for SJS in Adult RX Label for Motrin/Advil	1982	All of the above	Probable rate less than 1%	Addition to FPL for Motrin/Advil dated 1982

"Incidence less than 1% (Probable causal relationship)

"Skin and appendages " Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson's Syndrome, alopecia."

Table #2 : Accumulation of Knowledge of Risk of SJS/TEN in adults (1990 thru 1996)

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
NSAIDS (Adults) & SJS/TEN	1990-1996	Case reports of SJS/TEN	Supportive	FDA-FOI, WHO, CSM - Skin ADEs (1990-1996) Wyeth databases
NSAIDS (Adults) & SJS/TEN	1990-1996	Published case reports in Literature	Moderate	(1) Rouieau, JC, J Am Acad Derm, 23:pp.l039-58 (1990); (2) Roujeau, JC, Arch Dermatol. Vol. 126. pp. 37-42 (1990); (3) Strom, BL et. al.. Statistics in Medicine, vol. 10, pp. 565-576 (1991); (4) Stem, RS, et al., Immunology and Allergy

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
				Clinics of North America, Vol. 11, no. 3, pp. 493-507 (1991);(5) Schopf, et. al., Arch Dermatol, Vol. 127, pp. 839-842, (1991); (6) Roujeau, JC, et. al., Dermatology. 186:pp. 32-37 (1993); (7) Roujeau, JC, et. al., NEJM, Vol. 331, pp. 1272-1285 (1994); (8) Roujeau. JC. J Amer Acad Dermatol. Vol. 31, pp. 301302 (1994)
NSAIDS (Adults) & SJS/TEN	1995	Published or sponsored studies	Strong	Roujeau, J.C., et. al.. NEJM. Vol. 333, pp.1600-1607 (1995).
Ibuprofen (Adults) & SJS/TEN	1990-1996	Case Reports	Supportive	FDA-FOI, WHO, CSM - Skin ADEs (1990-1996) McNeil & Wyeth databases
Ibuprofen (Adults) & SJS/TEN		Published case reports in Literature	Supportive	(1) Roujeau, JC, Arch Dermatol, Vol. 126, pp. 3742 (1990); (2) Strom, BL et. al., Statistics in Medicine, vol. 10, pp. 565-576 (1991); (3) Strom, BL et. al., Arch Dermatol, Vol. 127, pp. 831-838 (1991); (4) Halpem, SM, et. al., Adverse Drug React. Toxicol Rev., 12 (2): pp. 107-128 (1993); (5) Roujeau, JC, et. al. NEJM, Vol. 331, pp. 1272-1285 (1994); (6) Halpern, SM, et. al., Arch Dermatol., vol. 130, pp. 259-60 (1994)
Ibuprofen (Adults) & SJS/TEN		Published or sponsored studies	Moderate	Roujeau. JC. et. al.. NEJM. Vol. 333, pp.1600-1607 (1995).
"Probable Causal	1994	All of the above	Probable rate less than 1%	Addition to FPL for Motrin/Advil dated

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
Relationship" for TEN in Adult RX Label for				1994
Motrin/Advil				
"Probable Causal Relationship" for TEN in Pediatric RX Label for Motrin/Advil	1994	All of the above	Probable rate less than 1%	Addition to FPL for Pediatric Motrin/Advil dated 1994
Pediatric OTC prep marketed	1996	N/A	N/A	N/A

Incidence less than 1% (Probable causal relationship)

"Skin and appendages " Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens- Johnson's Syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reactions. (1994 FPL)

Table 3: Accumulation of Knowledge of Risk of SJS/TEN in Adults associated

WHAT	WHEN"	HOW	How Strong	References
NSAIDS (Adults) & SJS/TEN	1997-2002	Case reports of SJS/TEN	Supportive	FDA-FOI & WHO databases McNeil & Wyeth databases
NSAIDs (Adults) & SJS/TEN	1998-2002	Published case reports/reviews of SJS/TEN in literature	Moderate	(1) Paul. CN. et al., J Burn Care & Rehab.. Vol. 19. **DD.** 321-33 (1998); (2) Bell, MJ, et. al.. J Rheumatol. 25:pp. 2026-2028 **(1998); (3)** Carucci, JA, et. al., Int. J Dermatol. Vol. 38. on. 228-239 **(1999); (4)** Fritsch, PO, et. al., Fitzpatrick's Dermatology in General Medicine, 5th. Ed., Vol. 1, Chap. 59, pp. 644-654 (1999);(5) Garcia-Doval;, I, et. al., Arch Dermatol., Vol. 136, pp. 323-327 (2000); (6) Wolkenstein, P, et. al., Dermatologic Clinics, Vol. 18,

WHAT	WHEN"	HOW	How Strong	References
				no. 3, pp. 485-495 (2000);(7) Svennson, CK, et. al., Pharmacol Rev., 53: pp. 357-379 (2000)
NSAIDs (Adults) &		Published or sponsored		
SJS/TEN		studies		
Ibuprofen (Adults) & SJS/TEN	1997-2002	Case reports of SJS/TEN	Supportive	FDA-FOI, WHO, McNeil & Wyeth databases
Ibuprofen (Adults) & SJS/TEN	1997-2002	Published case reports/reviews of SJS/TEN caused by ibuprofen	Moderate	(1) Salomon, D, et. al., Annals of Dermatology, 124 (Suppl.):S216-217 (1997); (2} Viard. I. et. al.. Journal of Science. Vol. 282, pp. 490-93 **(1998)**; (3) Becker, D. Lancet, Vol. 351, pg. 1417, **(1998)**; (4) Fritsch, PO. et. al., Fitzpatrick's Dermatology in General Medicine. 5th Ed.. Vol. 1, Chap. 59, pp. 644-654 (1999); (5) Garcia-Doval;, I, et. al.. Arch Dermatol.. Vol. 136, pp. 323-327 (2000); (6) Wolkenstein, P, et. al., Dermatologic Clinics. Vol. 18, no. 3, pp. 485-495 (2000)
Ibuprofen	2002	Published		

WHAT	WHEN"	HOW	How Strong	References
(Adults) & SJS/TEN		studies		
Significant subsequent evidence			Strong	Mockenhaupt, et. al., J Rheumatol. Vol. 30. pp. 2234-40 **(2003)**

Table #4 - Accumulation of Knowledge of Risk of SJS/TEN from NSAIDS/Ibuprofen in Pediatrics

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
Higher risk of severe rash in pediatrics	1994	Literature on Lamotrigine & other anti-convulsants	3 fold higher than adults	Dooley, 1994 Roujeau 1995 Besag, 1997 Guberman, 1999
Ibuprofen (Children) & SJS/TEN	1984 - 2002	Case reports	Supportive	FDA-FOI, WHO, McNeil & Wyeth databases
Ibuprofen (Children) & SJS/TEN	1984 - 2002	Published case reports in Literature	Strong (1999)	(1)); Roujeau, JC, J Am Acad Derm.. Vol. 23. pp. 1039-58 (1990); (2) Roujeau, JC. et. al.. NEJM. Vol. 331, pp. 1272-1285
				(1994); (3) Power,et. al., Ophthalmology. Vol. 102, pp. 1669-1676 (1995); (4) Srivastava, M, et. al., Gastroenterology. Vol. 115. pp. 743-746 (1998); (5) Sheridan. RL. et. al.. J Burn Care Rehab.. Vol. 20. pp. 497-500 (1999) (6) Fritsch, PO, et. al., Fitzpatrick's Dermatology in

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
				General Medicine. 5th. Ed.. Vol. 1. Chap. 59, pp. 644-654 (1999); (7) Wolkenstein, P, et. al.. Dermatologic Clinics. Vol. 18. no. 3. pp. 485-495 (2000); (8) Sheridan, RL, et. al., Pediatrics, Vol. 109, pp. 74-78 (Jan. 2000); (9) Spies. M. et. al.. Pediatrics. Vol. 108, pp. 1162-1168 (2001)
Ibuprofen (Children) & SJS/TEN		Published or sponsored studies	Noninformative	BUFS (Lesko, 1995) CAMP (submitted in NDA supplement only)
Probable Causal Relationship to SJS in label Children's Rx Advil	1987	N/A	N/A	Addition to FPL for Pediatric Motrin/Advil dated 1987
Pediatric OTC prep marketed	1994	N/A	N/A	No SJS/TEN warning, nor any 'cease and seek MD" advice
Probable Causal Relationship to TEN in Rx /NDA label Children's Advil	1994			Addition to FPL for Pediatric Motrin/Advil dated 1994
Constant risk on continued exposure	2000		Strong	Garcia-Doval, 2000 Stem, 2000
Recent evidence on Ibuprofen & SJS/TEN	1999 & 2001	Published case-series	Extremely Strong	Sheridan, 1999 & 2001

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
(pediatrics)				
	2004			Taehian. M. J Pediatrics. Vol. 145, pp. 273-276 (2004)

The Severe Cutaneous Adverse Reaction (SCAR) study

The SCAR study was a huge multinational effort to determine the etiology and risk factors for the most severe of the cutaneous reactions. The methodology was published by Kelly et.al, (1995), with the results published by Roujeau et.al. (1995), Auquier-Dunant et.al. (2002), and Mockenhaupt et.al.,(2003). The Roujeau study identified cases then assessed exposure to all drugs. They found oxicam NSAIDS highly statistically significant but the proprionic acid NSAIDS, though having an increased point estimate, fell short of statistical significance. The point estimate for ibuprofen was 4.5 (2/245 or 0.0082 over 2/1147 or 0.0017) though statistical significance was not reached. This was clearly a signal in the adult population. Note that isoxicam was removed from the French marketplace after being associated with 13 cases of TEN (Roujeau JC, 1990). That followed the removal of benoxaprofen from the U.S. market in 1982 for toxicity that included cases of TEN (Stern 1984).

Mockenhaupt et.al. (2003) reported on a component of the SCAR study, a population-based registry in Germany and on data from the US spontaneous reporting system. There were 373 diagnostically validated cases in the multi-16

national case-control component and 950 in the German registry. The same questionnaire and definitions were used in both of these component studies.

In the case-control component 112 of 373 were exposed to an NSAID (excluding aspirin). The oxicams (RR 34, 95% CI: 11-105) were strongly associated with the greatest increase in risk for SJS and TEN. Of the non-oxicam NSAIDs with sufficient numbers of exposed cases, only diclofenac and ibuprofen has significantly increased risks of SJS and TEN. The relative risk for ibuprofen was 5.3 (95% CI: 1.2-25). For the propionic acid NSAIDS (including ibuprofen), they estimated the excess risk to be less than one case in a million exposures. Given the number of children exposed to the pediatric formulations of OTC ibuprofen, the expected number of ibuprofen associated cases worldwide , even at 3 cases per million, could be sizable and of public health import.

The SCAR study (Roujeau et.al., 1995, and Mockenhaupt et.al., 2003) clearly implicates all NSAIDS, in varied intensity, in a causal relationship with SJS/TEN. Based solely on the SCAR studies, Roujeau, et. al.'s paper signaled ibuprofens' causal relationship, and Mockenhaupt, et. al.'s paper validated its statistical significance.

C. The International Labeling/Proposed Labeling For Ibuprofen Provide More Warnings Relating To Serious Skin Reactions and The Need For Immediate Patient Care.

The Therapeutics Products Directorate commissioned an expert panel to draft an updated Guidance Document: **Guidance for Industry - Basic Product Monograph Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in 2003.**

Health Canada/TPD have proposed that all prescription NSAID manufacturers, including manufacturers of prescription ibuprofen products, would have to provide a specific warning about SJS and TEN in their respective package inserts. Comments were provided to Health Canada until September 9, 2003. Final implementation of this document is expected shortly. A copy of this Notice is attached hereto, and incorporated herein fully by reference as **Attachment 1.**

Labeling of foreign OTC ibuprofen products provides additional warnings that are not present on the domestic ibuprofen products. For example, McNeil/Johnson & Johnson market a product called Dolormin Ibuprofen Juice which is a non-prescription ibuprofen product sold in Germany. This product has a package insert that warns German consumers of side effects associated with this OTC product of rare but serious skin reactions, such as reddening and blister formation (e.g. erythema multiforme exudativum multiforme) which is bullous EM/SJS. Wyeth markets ibuprofen products known as Spalta in Germany that contain similar information to the public as well.

Further, Wyeth markets ibuprofen products in European countries, including the Netherlands that

specifically mention SJS and TEN on the OTC labeling.

American consumers deserve to be provided with appropriate warnings about serious life-threatening side effects as provided to foreign consumers. This foreign labeling was revealed in lawsuits that have been filed against the makers of Children's Motrin and Advil, however, the makers have insisted that these documents remain confidential and are not to be disclosed to anyone, except those persons associated with the law firms or their staff.

Petitioners are requesting that the FDA obtain such foreign labels and that they be translated into English and disseminated to the public without delay so that such information can be viewed by the American public.

D. Incidence and Frequency of all SJS and TEN events and for Ibuprofen are More Frequent and have a Higher Mortality Rate than Reye Syndrome

The Aspirin and Reye Syndrome experience taught us that a low frequency event which is also life-threatening is critically important when a large and otherwise healthy population is exposed to a discretionary drug product. For decades, "Baby aspirin" was very important for treatment of childhood fevers. When a safer alternative that was just as effective, acetaminophen (APAP), was marketed, "Baby aspirin" became discretionary though still widely used. When the association with Reye Syndrome was discovered and confirmed, it made the benefit-risk balance unacceptable. That

situation is almost exactly like this ibuprofen-SJS/TEN situation.

It is widely recognized that at therapeutic doses, APAP and Ibuprofen are equigesic. Many pediatric specialists use ibuprofen and APAP together or in alternating regimens to break high fever. Some specialists consider ibuprofen superior in these cases of high fever.

Analgesic-induced Reye syndrome is an exceedingly rare phenomenon and occurs more rarely than ibuprofen-induced SJS and TEN. The frequency of SJS has been estimated to be as high as 49-60/per million. (Strom, et. al., Statistics in Medicine, 1991) Moreover, a recent scientific paper has estimated that there are 5000 hospitalizations for patients with SJS and TEN that occur annually in the U.S. (Stem, RS, Pharmacoepidemiology and Drug Safety, 2005)

The absolute risk of Reye Syndrome has been estimated to be 6.2 per 100,000 (Cecil's Textbook of Medicine, 19th ed.), while the absolute risk for SJS associated with ibuprofen exposure was reported from The Boston University Fever Study to be 7.2 per 100,000. Obviously, when comparing the absolute risk between Reye Syndrome and SJS caused by ibuprofen in the pediatric population, one must also consider the difference between the mortality rates between these two diseases. Reye Syndrome has an estimated mortality rate of 10%, while SJS and TEN range from 5%-30%, and up to 80% for TEN. A child exposed to ibuprofen that develops SJS and TEN has s greater likelihood of

developing SJS and TEN, and is more likely to die from it than a child that develops Reye Syndrome from aspirin.

Yet, despite the lower risk of developing the disease and lower mortality rates, the FDA has required that all manufacturers of aspirin products contain a specific warning about Reye Syndrome, but they have not required any such warnings about SJS and TEN. The FDA must act now on these issues in order to serve the public's health in protecting American adults and children from the substantial risk of harm posed by SJS and TEN associated with ibuprofen and NSAIDs, not to mention the extraordinary healthcare costs associated with treating these diseases and the economic impact it has on causing permanent disability to American people afflicted with SJS and TEN.

E. Conclusion and Remedies Sought by Petitioners

The Kiss family is petitioning the FDA after their three year-old daughter Heather Kiss, died from toxic epidermal necrolysis caused by Children's Advil on March 17, 2003. Other parents of children who suffered permanent injuries from SJS and TEN associated with Children's Motrin and Advil are also joining the Kiss family in support of this petition. Additionally, scientists who are familiar with the regulatory history of McNeil Pharmaceutical and Wyeth Consumer healthcare's pediatric ibuprofen products, and the scientific literature regarding SJS and TEN, believe that there is major public health problem at issue with SJS and TEN associated with

ibuprofen products that needs to be addressed immediately to protect the American public from the harm posed in the use of ibuprofen products without an adequate warning and instructions regarding the risk of SJS and TEN associated with ibuprofen.

Unlike labeling employed outside the U.S., the U.S. labeling does not provide even minimal information relating to the increased risks described in the scientific literature, or the continued escalation in the numbers of adverse event reports describing serious skin reactions in adults and children receiving ibuprofen.

These reactions may quickly progress from a drug eruption and/or fever to the severe, life-threatening and fatal events associated with Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Toxic Epidermal Necrolysis has a reported mortality rate of 30%-80%. However, recognition of the early symptoms and the discontinuation of all ibuprofen products can prevent progression to SJS and TEN. Morbidity and mortality can be significantly reduced with early recognition and treatment (Wolkenstein and Revuz, Dermatologic Clinics, 2000). Garcia-Doval et al., in the Archives of Dermatology (2000) calculated an odds ratio for a better prognosis of 0.69 for each day the drug was withdrawn with drugs with a short half-life. This is particularly relevant for ibuprofen since it has a half-life of approximately 2 hrs under normal metabolic and pharmacokinetic conditions. SJS and TEN usually begin with non-specific flu-like symptoms (e.g. fever, sore throat, burning eyes) with the emergence of skin and

mucous membrane lesions within one day to a week. The dermatological symptoms usually present as a rash, itching skin and blisters that progress to more severe cutaneous lesions such as SJS and TEN, and systemic involvement if not recognized and the drug withdrawn.

It is therefore imperative that the U.S. product labeling alert physicians, patients, and consumers to the signs and symptoms relating to ibuprofen-induced SJS and TEN and provide instructions to prevent progression of these symptoms.

The petitioners request that the FDA Commissioner act immediately to require the labeling additions noted below. This action is especially critical because of ibuprofen's wide use in children and as OTC preparations.

- **Bolded Black Box Warning for Prescription Products:**

Serious Skin Reactions

Serious skin reactions including Erythema Multiforme.

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis have been associated with the use of NSAIDs, including ibuprofen. These events occur rarely and have been identified in U.S. and worldwide postmarketing safety surveillance programs and the scientific literature. These reactions are potentially life-threatening and fatal, but may be reversible if ibuprofen is discontinued immediately at the first sign of a rash, mucosal lesion or blisters (sores in mouth, throat, eyes, or genitalia), or if an unexplained or persistent fever occurs while taking ibuprofen. Patients should be advised to stop taking ibuprofen, if any of these symptoms occur and contact their physician immediately.

• Dear Doctor and Dear Healthcare Professional Letters

The Petitioners believe the gravity of the reported dermatologic events dictate health care providers be alerted to this information as soon as possible.

These letters should be provided to all U.S. prescribers because of the high use of ibuprofen in all age populations and as prescription and OTC products. Letters should also be sent to pharmacists, medical associations, hospitals (including critical care and burn centers) to allow the most rapid and

most extensive dissemination of this critical safety information. These letters should provide specific guidance to prescribers and patients for the detection of these events and the medical intervention necessary to halt their critical progression.

• Reconsideration of the OTC status of the pediatric formulation or, at minimum, changing the Labeling for OTC Ibuprofen Products

The FDA should either reconsider removing the pediatric or adult ibuprofen products from the market as over-the-counter- medications to prescription products under the supervision of a physician with amplified warnings and precautions in the revised package insert to warn about risks of SJS and TEN, or alternatively provide the following labeling changes to the OTC labeling for ibuprofen products:

Warnings **(to follow "Allergy alert")**

Serious Skin Reactions: Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate medical attention if any of these symptoms develop while taking ibuprofen.

Stop use and ask a doctor if

■ a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

III. Environmental Impact Statement

The Petitioners believe the actions requested in this Petition provide no significant environmental impact. The requested actions will not introduce any substance into the environment and is categorically excluded pursuant to 21 CFR 25.30.

IV. Economic Impact Statement

This information is only to be submitted when requested by the Commissioner following a review of this petition.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

(signed)
Roger E. Salisbury, M.D.
Professor of Surgery Chief,
Plastic Surgery at New York Medical College
Director, Burn Unit
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Valhalla, NY

(signed)
Steven Pliskow, M.D., FACOG, FACFE
Clinical Professor of Obstetrics and Gynecology
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Randall Tackett, Ph.D.
Professor
Department of Clinical and Administrative
Pharmacy University of Georgia,
Athens, Georgia

(signed)

Darlene and Andrew Kiss
Aberdeen, NJ
Three-year old daughter, Heather, died after taking Children's Advil (Ibuprofen) from Toxic Epidermal Necrolysis

(signed)
Christy and Steven Esnard, Houston, Texas
5 year-old daughter suffered permanent injuries after taking Children's Motrin (Ibuprofen) from Stevens Johnson Syndrome

DEPARTMENT OF HEALTH & HUMAN SERVICES

June 22 2006

Food and Drug Administration
Rockville MD 20857

Roger E, Salisbury, MD
Professor of Surgery, Chief of Plastic Surgery
New York Medical College
Director of Burn of Center Westchester Medical Center
Macy Pavillion
Valhalla, New York 10595

Re: Docket No. 2005P-0072/CP1

Dear Dr. Salisbury:

This letter responds to your citizen petition dated February 15, 2005, submitted an behalf of seven petitioners. You request that the Food and Drug Administration (FDA) take the following actions:

1. conduct a risk assessment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with the use of ibuprofen products;
2. conduct an investigation into manufacturers' withholding of critical safety information regarding the risks

of SJS and TEN associated with ibuprofen products; and

3. require manufacturers of ibuprofen to amplify their prescription and over-the-counter (OTC) labeling to adequately warn prescribers, healthcare professionals, and consumers of the risks of SJS and TEN.

For the reasons that follow, your petition is granted in part and denied in part.

I. BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) is a class of drugs that includes ibuprofen products. Ibuprofen products are available by prescription and OTC. Prescription and OTC ibuprofen are indicated for temporary relief of minor aches and pains and reduction of fever. In addition, prescription ibuprofen is indicated for relief of mild to moderate pain; relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis; and treatment of primary dysmenorrhea.

NSAIDs, including ibuprofen, are known to cause SJS and TEN, as reflected in the labeling of NSAIDs, including ibuprofen prescription labeling. While adverse skin reactions to drugs are frequent, serious adverse cutaneous reactions are not. SJS and TEN are within a spectrum of the same disease and are severe drug eruptions. Prompt recognition of the onset of symptoms, such as the appearance of rash or blisters on the skin, and withdrawal of the suspected

drug can minimize the effects of SJS/TEN and improve prognosis.[1]

In 2005, FDA engaged in a comprehensive review of the risks and benefits, including the risks of SJS and TEN, of all approved NSAID products, including ibuprofen. This comprehensive risk-benefit assessment focused primarily on potential cardiovascular and gastrointestinal safety concerns associated with COX-2 selective and non-selective NSAIDs. On April 6, 2005, FDA issued a press release and public health advisory announcing a series of actions to alert consumers and healthcare practitioners about the risks associated with the use of'COX-2 and NSAID products. FDA also posted a Decision Memo entitled "Analysis and Recommendations for Agency Action—COX-2 Selective and Non-selective NSAIDs" (www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf (Decision Memo). In its Decision Memo, FDA emphasized the public health importance of maintaining a range of options in the NSAID class from which physicians and patients may choose (Decision Memo at 11-13).

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[1] Fritsch, P.O., and A. Sidoroff, "Drug-Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *American Journal of Clinical Dermatology*, 1(6):349-360, Nov-Dec 2000; WoIkenstein P., and J. Revuz, "Drug-Induced Severe Skin Reactions. Incidence, Management and Prevention," *Drug Safety*, l3(1):56-68, July 1995; and Mockenhaupt, M., et al., "The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Nonsteroidal Anti-Inflammatory Drugs: A Multinational Perspective," *Journal of Rheumatology*, 30 :2234-2240, 2003.

The Agency's actions included issuing supplemental request letters to manufacturers of all NSAIDs asking that they make labeling changes to their products. In addition, FDA posted labeling templates for both the prescription and OTC NSAIDs and a template for a medication guide to be distributed with the entire class of prescription products. The labeling changes resulting from this comprehensive analysis include additional warnings regarding the risks of SJS and TEN (discussion in section II.C of this response). For a comprehensive posting of FDA's actions regarding NSAIDs, see our Web site at www.fda.gov/cder/drug/infopage/COX2.

II. DISCUSSION

A. Review of Adverse Event Reporting System (AERS) Data

You have requested that FDA conduct a thorough assessment of the risks of developing SJS or TEN associated with the use of prescription and OTC ibuprofen drug products (Petition at 1). FDA uses a number of methods to monitor the safety of marketed drugs, including review of clinical trials submitted to FDA for marketing approvals, review of other clinical studies available in the scientific literature, and review of the Adverse Event Reporting System (AERS) surveillance database implemented in 1997. As you recognize in your petition (based on the thorough citation of the clinical studies from publicly available literature (Petition at 10-17)), clinical trials provide strong evidence of the potential for adverse reactions associated with a particular drug.

You state that the frequency of SJS has been estimated to be as high as 49 to 60 cases per million (Petition at 20, citing Strom et al., *Statistics in Medicine*, 1991). You also state that the incidence of SJS and TEN is approximately 6 or 7 cases per 100,000, citing the Boston University Fever Study (BUFS) and *Cecil Textbook of Medicine*, 19th edition (Petition at 20).[2]

We believe that the available evidence, including but not limited to adverse events reports, indicates that the incidence of SJS and TEN is less than the cited estimate of 6 or 7 cases per 100,000. Based on our review of the literature (including BITFS, Children's Analgesic Medicine Project and other, more recent study reviews, including those cited in the Petition at 10-17), we estimate the overall incidences of SJS and TEN range from 1.2 to 6 per million per year and 0.4 to 1.2 per million per year, respectively.[3]

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[2] Note that *Cecil Textbook of Medicine*, 22d Ed., 2004, does not include an incidence rate for SJS or TEN.

[3] See Wolkenstein, P., et al.; Mockenhaupt, M., et al., *supra* note 1; Chan, H.L, et al., "The Incidence of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis. A Population-Based Study with Particular Reference to Reactions Caused by Drugs Among Outpatients," *Archives of Dermatology*, 126(1):43-47, 1990; Strom, B.L, et al., "A Population-Based Study of Stevens-Johnson Syndrome. Incidence and Antecedent Drug Exposures," *Archives of Dermatology*, 127(6):831-838, 1991; Rzany, B. et al., "Epidemiology of Erythema Exsudativum Multiforme Majus, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis in Germany (1990-1992): Structure and Results of a Population-Based Registry," *Journal of Clinical Epidemiology*, 49(7):796-773, 1996. It is worth noting that the oxicam NSAIDs are nearly always implicated with a higher risk than the propionic NSAIDs (which includes Ibuprofen). In one study, the multivariate relative risk for the group of propionic acid NSAIDs did not reach statistical significance. Roujeau, J.C., et al., "Medication Use

BUFS, which was reviewed by FDA in 1995 during the prescription-to-OTC switch of ibuprofen suspension, was a randomized, active drug-controlled, double-blind, practitioner-based trial in 83,915 febrile children, ages 6 months to 12 years. The study was specifically designed to assess the safety of ibuprofen 5 milligrams (mg)/kilograms (kg) and ibuprofen 10 mg/kg relative to acetaminophen 12 mg/kg in the treatment of febrile children. A total of 55,785 patients received ibuprofen suspension (27,948 received a 5 mg/kg dose and 27,837 received a 10 mg/kg dose) and 28,130 received acetaminophen 12 mg/kg. While there were no cases of SJS or TEN reported during the 4-week follow-up study, there were four cases of erythema multiforme reported (one in the acetaminophen group, one in the ibuprofen 5 mg/kg group, and two in the ibuprofen 10 mg/kg group).[4] The incidences of one per 28,130 in

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and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *New England Journal of Medicine*: 333(24):1600-7, 1995.

[4] Erythema multiforme is a skin reaction in the same family as SJS and TEN. Classification of these reactions in five categories is based on clinical criteria proposed by Roujeau:

* Bullous erythema multiforme, detachment below 10% of the body surface area (BSA) plus localized typical targets or raised atypical targets

* SJS, detachment below 10% of the BSA plus widespread erythematous or purpuric macules or flat atypical targets

* Overlap SJS/TEN, detachment between 10% and 30% of the BSA plus widespread purpuric macules or flat atypical targets

* TEN with spots, detachment above 30% of the BSA plus wide-spread purpuric macules or flat atypical targets

* TEN without spots, detachment above 10% of the BSA with large epidermal sheets and without any purpuric macules or target

Roujeau, J.C., "The Spectrum of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Clinical Classification," *Journal of*

the acetaminophen group, one per 27,948 in the 5 mg/kg ibuprofen group, and two per 27,837 in the l0, mg/kg ibuprofen group were extrapolated into 3.6, 3.6, and 7.2 per 100,000 respectively. On further review of these four cases, it is not clear whether they were caused by the study drugs, by other concomitantly used drugs (such as antibiotics), or by the disease for which the patient received drug treatment.

In addition, in response to your request, we reviewed the U.S. postmarketing adverse event reports of SJS and TEN in association with the use of ibuprofen products. Adverse event cases gathered in the AERS database come from different sources, including serious adverse events reported directly to the manufacturers of the drugs.

AERS can be used to very effectively identify serious, unexpected rare events that were not detected during the drug's clinical trials, but the system also has well-known limitations. Challenges to using AERS include: (1) AERS reports are not systematically collected; (2) AERS reports are often missing important clinical information; (3) patients may have other drug exposures that make attribution difficult; and (4) reporters can be influenced by media or other external pressures.

We searched the AERS database for domestic reports of SJS and TEN associated with all ibuprofen products (prescription and OTC) during its marketing history from 1975 through March 2005.

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lnvestigative Dermatology, 102(6):28S-30S, 1994.

The AERS database search retrieved 88 cases, of which 49 were possibly related to the use of ibuprofen products: 31 cases reported SJS and 18 cases reported TEN. There was no noticeable trend over the years in reporting of adverse events given the small number of reports received per year. Of the 49 cases, 13 reported the use of -an OTC ibuprofen product and 17 reported the use of a prescription ibuprofen product; the remaining cases did not specify this information. The age of patients ranged from 16 months to 81 years with the median age of 23 years. There were 21 pediatric cases (less than or equal to 17 years old) . Thirty-one cases reported the concomitant use of other medications, of which 10 cases reported the concomitant use of a co-suspect drug that has been associated with SJS and/or the development of TEN. The median time to onset of the event was 3 days with a range from one dose to 10 weeks. The doses ranged from 200 mg to 3200mg/day. Serious outcomes included 5 deaths and 38 hospitalizations. Three cases of death, including one identified in your petition, may have been related to TEN and the use of ibuprofen. The causes of death in the other two cases were not specified, and again, these cases involved co-suspect drugs.

Putting these numbers in context, there are approximately 29 million prescriptions dispensed per year in the U.S. retail setting for prescription single-ingredient ibuprofen tablets, oral liquids, and suspensions, or combination products containing

ibuprofen[5] and probably more than 100 million users of OTC ibuprofen per year.

We recognize that there is a risk of SJS and TEN associated with the use of ibuprofen products. However, our analysis of AERS and other data indicates that the risk is not as great as you assert in the petition.

In your petition, you compare the incidence and frequency of SJS and TEN associated with the use of ibuprofen products with the incidence and frequency of Reye's syndrome associated with the use of aspirin and conclude that the benefit-risk balance is analogous (Petition at 19-21).

First, as discussed, we believe that the risks, in terms of incidence and frequency, of SJS and TEN associated with ibuprofen are significantly less than cited in the petition. The incidence of Reye's syndrome before 1982 (prior to the Reye's syndrome warning implementation for salicylate-containing drug products) was greater than is the incidence of SJS and TEN. Specifically, it was estimated that overall incidence of Reye's syndrome in persons under 18 years of age was 0.37 to 4.7 per 100,000, and in persons who contracted influenza B was 30 to 60 per 100,000.[6] This risk was significantly greater than the estimated 1.2 to 6 per million per year for SJS and the estimated 0.4 to 1.2 per million per year for TEN.

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[5] IMS Health, National Prescription Audit *Plus*™, Years 2002, 2003 and 2004, Data Extracted August 2005.

[6] "Reye's Syndrome—Epidemiological Considerations," *Lancet*, 1(8278):941-943, 1982.

In addition, you claim that the mortality rate for SJS ranges from 5 to 30 percent and up to 80 percent for TEN (Petition at 20). Based on our review of the literature, SJS is fatal in approximately 5 percent of incidences and TEN is fatal in approximately 30 percent of incidences.[7] The mortality rate for Reye's syndrome reported to the Center for Disease Control (CDC) at the time of the Reye's syndrome warning implementation was between 20 and 30 percent.[8]

However, even if the frequency-rate and rate of fatality were comparable to that of Reye's syndrome and aspirin, we do not believe that Reye's syndrome offers an analogous benefit-risk balance. Although Reye's syndrome is a disease of unknown cause, we do know that it is precipitated by the use of aspirin during a viral illness, mainly chicken pox and influenza.[9] Therefore, Reye's syndrome is preventable, in the sense that we can warn people not to use aspirin if they may have a viral illness. SJS and TEN, on the other hand, are not associated with any particular risk factors and, therefore, are unpredictable. We can warn users to beware of the symptoms of SJS and TEN, but we do not know under what circumstances to avoid the use of ibuprofen or other NSAIDs altogether.

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[7] Wolkenstein, P., et al.; Mockenhaupt, M., et al., *supra* note 1; and *Cecil Textbook of Medicines*, 22d Ed., 2004.

[8] CDC, "Follow-up on Reye Syndrome-United States," *Morbidity and Mortality Weekly Report*, 29:321-322, 1980; CDC, "National Surveillance for Reye Syndrome, 1981: Update, Reye Syndrome and Salicylate Usage," *Morbidity and Mortality Weekly Report*, 31(5):53-60, 1982.

[9] *Id.* and Sullivan-Bolyai et al., "Epidemiology of Reye Syndrome," *Epidemiologic Reviews*, 3:1-26, 1981.

B. Manufacturers' Conduct

You state that manufacturers of ibuprofen drug products have withheld safety information regarding the risks of SJS and TEN associated with ibuprofen products and request FDA to conduct an investigation accordingly. You state that "McNeil and Wyeth have failed to provide the FDA full information regarding the safety issues surrounding serious skin reactions, including SJS/TEN that were not presented in their applications for their OTC pediatric formulations" (Petition at 9). However, you provide no evidence to support this allegation. In addition, we have no evidence that there is additional undisclosed safety information that was withheld by ibuprofen manufacturers . If you have any information to support this allegation, please provide it to us.

Ibuprofen products, whether OTC or prescription, are marketed only under a new drug application (NDA) or abbreviated NDA (ANDA). Therefore, manufacturers of ibuprofen must comply with the safety reporting requirements for approved NDAs and ANDAs (21 CFR 314.80 and 314.81). Under these regulations, manufacturers must report all serious, adverse drug experiences whether the ibuprofen is marketed as prescription or OTC. In either case, if a manufacturer receives a report of SJS or TEN associated with the use of a prescription or OTC product, it would be considered a serious, expected adverse drug experience and must be reported. SJS and TEN are categorized as "expected" events because they are listed in the current labeling

for the drug product. Therefore, manufacturers are required to submit reports they have received of SJS and TEN to FDA annually in periodic reports under § 314.80(c)(2). Again, we have no evidence that manufacturers are not complying with these reporting requirements. Therefore, we see no actionable allegation to pursue.

C. Communication of Risk Information

You request FDA to require additional warnings in the labeling of both prescription and OTC ibuprofen to warn prescribers and consumers about the risks of SJS and TEN associated with the use of ibuprofen. You request that FDA issue "Dear Doctor" and "Dear Healthcare Professional" letters to educate the healthcare community about these risks. In addition, you request that FDA obtain ibuprofen foreign labels, and that they be translated into English and disseminated to the public . Finally, with regard to OTC ibuprofen, you recommend that FDA reconsider the OTC status of the pediatric formulation of ibuprofen (Petition at l-2, 19-24).

As discussed in section I of this response, in April 2005, FDA issued a press release that included a statement about potential skin reactions associated with the use of NSAIDs and announced that the Agency is asking manufacturers of OTC NSAIDs to include a warning about potential skin reactions. In addition, FDA posted a public health advisory, a "question and answer" education tool that includes a question on SJS and potentially life-threatening skin reactions, supplemental request letters, and labeling templates (www.fdagov/cder/dru infopage/COX2). We

believe that this comprehensive effort responds to the actions that you have requested in your petition.

1. Prescription Ibuprofen

In your petition at 23, you recommend :the Agency take the following actions regarding ibuprofen prescription drug labeling and risk communication:

> * Add a bolded black box warning against erythema multiforme, SJS, and TEN, describing the associated symptoms, potential outcomes and recommended actions
>
> * Issue Dear Doctor and Dear Healthcare Professional letters

We agree that revisions to labeling are necessary to make more explicit the risks associated with SJS and TEN. Therefore, your request for labeling revisions has been granted. We have requested that manufacturers change the labeling for all NSAIDs, including ibuprofen, to include a description of early symptoms associated with SJS and TEN in the **Skin Reactions** section in **WARNINGS**, as follows:

> **Skin Reactions**
>
> NSAIDs, including TRADENAME, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at

> the first appearance of skin rash or any other sign of hypersensitivity.

In addition, we have requested that the **Information for Patients** section of **PRECAUTIONS** read as follows:

> TRADENAME, like other NSAlDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

However, we do not believe that the risk-benefit balance warrants inclusion of a bolded black box warning. Therefore, this aspect of your request is denied.

As discussed in section I of this response, we conducted a thorough analysis of risks associated with all NSAIDs. As a result of that analysis, we concluded that the cardiovascular risks and the gastrointestinal risks rise to the level warranting a bolded black box warning for all NSAID products. For a template of the bolded black box warning for NSAIDs, see www.fda.gov/cder/drug/

infopage/COX2/NSAIDRxTemplate.pdf. FDA compared the risks of SJS/TEN associated with the different types of NSAID products and concluded that there was a greater risk with certain of the COX-2 selective NSAID products than with the older, non-selective NSAID, ibuprofen products. (See section II.A of this document for a discussion of the risks associated with ibuprofen products.) As a result, two of the COX-2 selective NSAID products (valdecoxib and rofecoxib) have been withdrawn from marketing. However, FDA concluded that for ibuprofen products, the labeling changes proposed are appropriate and that a boxed warning is not warranted at this time.

As part of this comprehensive risk-benefit analysis, FDA decided to require a NSAID Medication Guide under 21 CFR part 208 that accompanies each prescription dispensed (http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.htm) . One of the serious side effects listed within the Medication Guide is "life-threatening skin reactions." In addition, it directs patients to "Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms," which include "itching," "flu-like symptoms," and "skin rash or blisters with fever."

We believe that the public health advisory, press announcements, and educational tools that we have developed, within the context of a comprehensive prescriber and consumer awareness and education campaign, are the most effective mechanisms to alert the healthcare community and NSAID consumers

about the serious risks associated with these products.

2. OTC Ibuprofen

You recommend that FDA reconsider the OTC` status of the pediatric formulation of ibuprofen or, at a minimum, add the following changes to ibuprofen OTC labeling:

> * In the "***Warnings***" of the labeling: "**Serious Skin Reactions**: Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate attention if any of these symptoms develop while taking ibuprofen."
>
> * In the "***Stop use and ask a doctor if***": "a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis."

(Petition at 23-25).

We agree that the labeling for OTC NSAIDs, including all ibuprofen products, should be improved to warn consumers about the risks of severe skin reactions associated with OTC ibuprofen products

(see Decision Memo at 15-16). As a result, we have requested that manufacturers include under the ***Allergy alert*** subheading the symptoms associated specifically with SJS and TEN. We do not believe that it is useful to include the specific terms *SJS*, *TEN*, or *erythema multiforme*, *Stevens-Johnson syndrome*, and *toxic epidermal necrolysis* in the OTC label because most consumers are unfamiliar with these terms. In addition, effective OTC labeling communicates warning information in a manner that consumers can quickly and easily identify and understand. Consequently, we believe a description of symptoms is more appropriate. Therefore, prominently displayed under the ***Allergy alert*** subheading in the Drug Facts Label, the labeling will include:

* skin reddening

* rash

* blisters

In addition, under the ***Allergy alert*** subheading, the labeling will state: "If an allergic reaction occurs, stop use and seek medical help right away." We believe that adding these symptoms to the ***Allergy alert***, with advice to stop use and seek medical attention immediately, will alert and educate consumers to the nature of the allergic reactions associated with SJS and TEN. Further, we intend to continue our consumer education efforts regarding the safe and effective use of OTC pain relievers.

We disagree, however, with your request that we reconsider the OTC status of the pediatric

formulation of ibuprofen. As discussed above, we believe that the incidence of SJS or TEN is not as great as cited. We believe that the overall benefit versus risk profile for ibuprofen products remains very favorable when they are used according to the labeled instructions. It is in the interest of the public health to maintain in the pediatric OTC market a range of therapeutic options for the short-term relief of pain. Further, as discussed in greater detail in the Decision Memo (at 15), other available OTC drugs for short-term relief of pain and fever can also be associated with serious, potentially life-threatening adverse events in certain settings and patient populations.

Finally, you request FDA to obtain foreign labels, translate them into English, and disseminate them to the American public (Petition at 19). We received some foreign OTC ibuprofen product labeling and recognize that there is variation in the information provided internationally. However, as a result of our extensive, comprehensive revision of both OTC and prescription labeling for all NSAID products, we believe that the revised labeling templates for both OTC and prescription ibuprofen products most appropriately communicate the risks and benefits associated with their use. Enclosed are: (1) the labeling template for the new Drug Facts label for adult and pediatric OTC ibuprofen drug products; (2) the labeling template for ibuprofen prescription labeling; and (3) the Medication Guide that must accompany ibuprofen prescription drug products.

III. CONCLUSION

For the above stated reasons, your petition is granted in part and denied in part.

Sincerely,
(signed)
Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research

Enclosures

ADULT DRUG FACTS LABEL:

Drug Facts
Active ingredient (in each [insert dosage unit]) ***Purpose*** [*insert* active ingredient] XXX mg (NSAID)*……..Pain reliever/ *nonsteroidal anti-inflammatory drug fever reducer
Uses * [add NDA approved uses]
Warnings **Allergy alert**: [insert active ingredient] may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: * hives * facial swelling * asthma (wheezing) * shock * skin reddening * rash *blisters If an allergic reaction occurs, stop use and seek medical help right away. **Stomach bleeding warning**: This product contains a nonsteroidal antiinflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you: * are age 60 or older * have had stomach ulcers of bleeding problems * take a blood thinning (anticoagulant) or steroid drug * take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] * have 3 or more alcoholic drinks every day while using this product * take more or for a longer time than directed
Do not use * if you have ever had an allergic reaction to any other pain reliever/fever reducer * right before or after heart surgery
Ask a doctor before use if you have

* problems or serious side effects from taking pain relievers or fever reducers * stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain * ulcers * bleeding problems * high blood pressure * heart or kidney disease * taken a diuretic * reached age 60 or older
Ask a doctor or pharmacist before use if you are * taking any other drug containing an NSAID (prescription or nonprescription) * taking a blood thinning (anticoagulant) or steroid drug * under a doctor's care for any serious condition * taking any other drug
When using this product * take with food or milk if stomach upset occurs * long term continuous use may increase the risk of heart attack or stroke
Stop use and ask a doctor if * you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. * pain gets worse or lasts more than 10 days * fever gets worse or lasts more than 3 days * stomach pain or upset gets worse or lasts * redness or swelling is present in the painful area, * any new symptoms appear
If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use [NSAID active

ingredient] during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. **Keep out of reach of children**. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions *** do not take more than directed** *** the smallest effective dose should be used** * do not take longer than 10 days, unless directed by a doctor (see Warnings) * [**add NDA approved directions**]
Other information * [storage conditions]
Inactive ingredients [list ingredients in alphabetical order]
Questions or comments? call 1-800-XXX-XXXX: [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 1 l PM EST; weekends 9AM to 11PM, EST

PEDIATRIC DRUG FACTS LABEL

(For Products Labeled Only for Children Under 12 Years of Age)

Drug Facts
Active ingredient (in each [insert dosage unit]) ***Purpose*** Ibuprofen XXX mg (NSAID)*.....Pain reliever/ *nonsteroidal anti-inflammatory drug fever reducer
Uses * [add NDA approved uses]
Warnings **Allergy alert**: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: * hives * facial swelling * asthma (wheezing) * shock * skin reddening * rash *blisters If an allergic reaction occurs, stop use and seek medical help right away. **Stomach bleeding warning**: This product contains a nonsteroidal antiinflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the child: * has had stomach ulcers or bleeding problems * takes a blood thinning (anticoagulant) or steroid drug * takes other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] * takes more or for a longer time than directed **Sore throat warning**: Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult doctor promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by doctor. [For products with an approved "sore throat" indication]
Do not use

* if the child has ever had an allergic reaction to any other pain reliever/fever reducer * right before or after heart surgery
Ask a doctor before use if the child has * problems or serious side effects from taking pain relievers or fever reducers * stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain * ulcers * bleeding problems * not been drinking fluids * lost a lot of fluid due to vomiting or diarrhea * high blood pressure * heart or kidney disease * taken a diuretic
Ask a doctor or pharmacist before use if the child is * taking any other drug containing an NSAID (prescription or nonprescription) * taking a blood thinning (anticoagulant) or steroid drug * under a doctor's care for any serious condition * taking any other drug
When using this product * take with food or milk if stomach upset occurs * long term continuous use may increase the risk of heart attack or stroke
Stop use and ask a doctor if * the child feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding. * stomach pain or upset gets worse or lasts * the child does not get any relief within first day (24 hours) of

treatment * fever or pain gets worse or lasts more than 3 days * redness or swelling is present in the painful area, * any new symptoms appear
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions *** this product does not contain direction or complete warnings for adult use** *** do not give more than directed** *** the smallest effective dose should be used** * do not give longer than 10 days, unless directed by a doctor (see Warnings) * [add NDA approved directions]
Other information * [storage conditions]
Inactive ingredients [list ingredients in alphabetical order]
Questions or comments? call 1-800-XXX-XXXX: [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 1 l PM EST; weekends 9AM to 11PM, EST

PRINCIPAL DISPLAY PANEL:

Proprietary Name (if used) Established name (NSAID), XXX mg Pain reliever/fever reducer

OR

Proprietary Name (if used) Established name XXX mg Pain reliever/fever reducer (NSAID)

Proposed NSAID Package Insert Labeling Template[1]
(Revised XXX/05)

TRADENAME (Established name which should always include dosage form) Strength

Cardiovascular Risk

* NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

* TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

* NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**) .

DESCRIPTION- No change

[1] Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

CLINICAL PHARMACOLOGY- No change

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of TRADENAME and other treatment options before deciding to use TRADENAME. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

TRADENAME is indicated:

* For reduction of fever [in patients age]

* For relief of mild to moderate pain [in patients age]

* For relief of signs and symptoms of juvenile arthritis.

* For relief of the signs and symptoms of rheumatoid arthritis

* For relief of the signs and symptoms of osteoarthritis.

* For treatment of primary dysmenorrhea.

* For acute or long-term use in the relief of signs and symptoms of the following:

1. Ankylosing spondylitis
2. Acute painful shoulder (Acute subacromial bursitis/supraspinatus tendinitis)
3. Acute gouty arthritis

Put in the product specific indication(s)

CONTRAINDICATIONS

TRADENAME is contraindicated in patients with known hypersensitivity to GENERIC NAME.

TRADENAME should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS - Anaphylactoid Reactions**, and **PRECAUTIONS - Preexisting Asthma**) .

TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CU) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms.

Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including TRADENAME, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events.

Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including TRADENAME, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. TRADENAME should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including TRADENAME, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with *a prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI

events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal antiinflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly . Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of TRADENAME in patients with advanced renal disease. Therefore, treatment with TRADENAME is not recommended in these patients with advanced renal disease. If TRADENAME therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to TRADENAME. TRADENAME should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS - Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including TRADENAME, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first

appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

TRADENAME cannot be expected to substitute far corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of TRADENAME in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including TRADENAME. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of

severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with TR.ADENAME. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), TRADENAME should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including TR.ADENAME. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including TRADENAME, should have their hemoglobin or hematoerit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving TRADENAME who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, TRADENAME should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

l. TRADENAME, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should he apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).

2. TRADENAME, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning, symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation**) .
3. TRADENAME, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat) . If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).
7. In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, TRADENAME should be discontinued.

Drug Interactions

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin

[When TRADENAME in administered with aspirin, its protein binding is reduced, although the clearance of free TRADENAME is not altered. The clinical significance of this interaction is not known; however,] as with other NSAIDs, concomitant administration of GENERIC NAME and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide

Clinical studies, as well as post marketing observations, have shown that TRADENAME can reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction an renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased

by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Drug/Laboratory Test Interactions

Only if positive interactions have been observed. (See 201.57(f)(4)(N).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Usually only if significant findings have been observed. (See 201.57(f)(5))

Pregnancy

Teratogenic Effects. Pregnancy Category C.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental

abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of TRADENAME on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs axe excreted in human-milk and because of the potential for serious adverse reactions in nursing infants from TRADENAME, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of ??? [have, have not] been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older) .

ADVERSE REACTIONS- No change

OVERDOSAGE- No change

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of TR.ADENAME and other treatment options before deciding to use TRADENAME. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with TRADENAME, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of ????, the recommended dose is ??? mg given orally ?? times per day.

[**Different dose strengths and formulations (i.e., capsules, tablets, suspensions) of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing {formulation (type, strength)}.**]

HOW SUPPLIED- No change

Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs
(NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

* with longer use of NSAID medicines
* in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

* can happen without warning symptoms
* may cause death

The chance of a person getting an ulcer or bleeding increases with:

* taking medicines called "corticosteroids" and "anticoagulants"
* longer use

* smoking

* drinking alcohol

* older age

* having poor health

NSAID medicines should only be used:

* exactly as prescribed

* at the lowest dose possible for your treatment for the shortest time needed

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What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are use to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

* different types of arthritis

* menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

* if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine

* for pain right before or after heart bypass surgery

Tell your healthcare provider:

* about all of your medical conditions.

* about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**

* if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**

* if you are breastfeeding. **Talk to your doctor**.

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:

* heart attack
* stroke
* high blood pressure
* heart failure from body swelling (fluid retention)
* kidney problems including kidney failure
* bleeding and ulcers in the stomach and intestine
* low red blood cells (anemia)
* life-threatening skin reactions
* life-threatening allergic reactions
* liver problems including liver failure
* asthma attacks in people who have asthma

Other side effects include:

* stomach pain
* constipation
* diarrhea
* gas
* heartburn
* nausea
* vomiting
* dizziness

Get emergency help right away if you have any of the following symptoms:

* shortness of breath or trouble breathing
* chest pain
* weakness in one part or side of your body
* slurred speech
* swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

* nausea
* more tired or weaker than usual
* itching
* your skin or eyes look yellow
* stomach pain
* flu-like symptoms
* vomit blood

* there is blood in your bowel movement or it is black and sticky like tar
* unusual weight gain
* skin rash or blisters with fever
* swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

* Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
* Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL

Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

This Medication Guide has been approved by the U.S. Food and Drug Administration.

U.S. Constitution
Article VI, cl. 2

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

United States Code Annotated
Title 21. Food and Drugs
Chapter 9. Federal Food, Drug, and Cosmetic Act
Subchapter V. Drugs and Devices
Part A. Drugs and Devices

§ 355. New Drugs

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(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5)

evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data

and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for premarket approval of a drug.

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration,
Department of Health and Human Services
Subchapter A. General
Part 10. Administrative Practices and Procedures
Subpart B. General Administrative Procedures

§ 10.25. Initiation of administrative proceedings

An administrative proceeding may be initiated in the following three ways:

(a) An interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action. A petition must be either:

> (1) In the form specified in other applicable FDA regulations, e.g., the form for a color additive petition in § 71.1, for a food additive petition in § 171.1, for a new drug application in § 314.50, for a new animal drug application in § 514.1, or
>
> (2) in the form for a citizen petition in § 10.30.

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Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration,
Department of Health and Human Services
Subchapter A. General
Part 10. Administrative Practices and Procedures
Subpart B. General Administrative Procedures

§ 10.30. Citizen petition.

(a) This section applies to any petition submitted by a person (including a person who is not a citizen of the United States) except to the extent that other sections of this chapter apply different requirements to a particular matter.

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(d) An interested person may submit comments to the Division of Dockets Management on a filed petition, which comments become part of the docket file. The comments are to specify the docket number of the petition and may support or oppose the petition in whole or in part. A request for alternative or different administrative action must be submitted as a separate petition.

(e)(1) The Commissioner shall, in accordance with paragraph (e)(2), rule upon each petition filed under paragraph (c) of this section, taking into consideration (i) available agency resources for the category of subject matter, (ii) the priority assigned to the petition considering both the category of

subject matter involved and the overall work of the agency, and (iii) time requirements established by statute.

(e)(2) Except as provided in paragraph (e)(4) of this section, the Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition. The response will either:

> (i) Approve the petition, in which case the Commissioner shall concurrently take appropriate action (e.g., publication of a Federal Register notice) implementing the approval;
>
> (ii) Deny the petition; or
>
> (iii) Provide a tentative response, indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information. The tentative response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished.
>
> (3) The Commissioner may grant or deny such a petition, in whole or in part, and may grant such other relief or take other action as the petition warrants. The petitioner is to be notified of the Commissioner's decision. The decision will be placed in the public docket

file and may also be in the form of a notice published in the Federal Register.

(4) The Commissioner shall furnish a response to each petitioner within 90 days of receipt of a petition filed under section 505(j)(2)(C) of the act. The response will either approve or disapprove the petition. Agency action on a petition shall be governed by § 314.93 of this chapter.

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration,
Department of Health and Human Services
Subchapter C. Drugs: General
Part 201. Labeling
Subpart C. Labeling Requirements for over–the–Counter Drugs

§ 201.66. Format and content requirements for over-the-counter (OTC) drug product labeling.

(a) Scope. This section sets forth the content and format requirements for the labeling of all OTC drug products. Where an OTC drug product is the subject of an applicable monograph or regulation that contains content and format requirements that conflict with this section, the content and format requirements in this section must be followed unless otherwise specifically provided in the applicable monograph or regulation.

(b) Definitions. The following definitions apply to this section:

(1) Act means the Federal Food, Drug, and Cosmetic Act (secs. 201 et seq. (21 U.S.C. 321 et seq.)).

(2) Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of

disease, or to affect the structure or any function of the body of humans. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

(3) Approved drug application means a new drug (NDA) or abbreviated new drug (ANDA) application approved under section 505 of the act (21 U.S.C. 355).

(4) Bullet means a geometric symbol that precedes each statement in a list of statements. For purposes of this section, the bullet style is limited to solid squares or solid circles, in the format set forth in paragraph (d)(4) of this section.

(5) Established name of a drug or ingredient thereof means the applicable official name designated under section 508 of the act (21 U.S.C. 358), or, if there is no designated official name and the drug or ingredient is recognized in an official compendium, the official title of the drug or ingredient in such compendium, or, if there is no designated official name and the drug or ingredient is not recognized in an official compendium, the common or usual name of the drug or ingredient.

(6) FDA means the Food and Drug Administration.

(7) Heading means the required statements in quotation marks listed in paragraphs (c)(2) through (c)(9) of this section, excluding subheadings (as defined in paragraph (a)(9) of this section).

(8) Inactive ingredient means any component other than an active ingredient.

(9) Subheading means the required statements in quotation marks listed in paragraphs (c)(5)(ii) through (c)(5)(vii) of this section.

(10) Drug facts labeling means the title, headings, subheadings, and information required under or otherwise described in paragraph (c) of this section.

(11) Title means the heading listed at the top of the required OTC drug product labeling, as set forth in paragraph (c)(1) of this section.

(12) Total surface area available to bear labeling means all surfaces of the outside container of the retail package or, if there is no such outside container, all surfaces of the immediate container or container wrapper except for the flanges at the tops and bottoms

of cans and the shoulders and necks of bottles and jars.

(c) Content requirements. The outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, shall contain the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(8) of this section, and may contain the information under the heading in paragraph (c)(9) of this section, in the order listed.

(1) (Title) "Drug Facts". If the drug facts labeling appears on more than one panel, the title "Drug Facts (continued)" shall appear at the top of each subsequent panel containing such information.

(2) "Active ingredient" or "Active ingredients" "(in each [insert the dosage unit stated in the directions for use (e.g., tablet, 5 mL teaspoonful) or in each gram as stated in §§ 333.110 and 333.120 of this chapter])", followed by the established name of each active ingredient and the quantity of each active ingredient per dosage unit. Unless otherwise provided in an applicable OTC drug monograph or approved drug application, products marketed without discrete dosage units (e.g., topicals) shall state the proportion (rather than the quantity) of each active ingredient.

(3) “Purpose” or “Purposes”, followed by the general pharmacological category(ies) or the principal intended action(s) of the drug or, where the drug consists of more than one ingredient, the general pharmacological categories or the principal intended actions of each active ingredient. When an OTC drug monograph contains a statement of identity, the pharmacological action described in the statement of identity shall also be stated as the purpose of the active ingredient.

(4) “Use” or “Uses”, followed by the indication(s) for the specific drug product.

(5) “Warning” or “Warnings”, followed by one or more of the following, if applicable:

(i) “For external use only” [in bold type] for topical drug products not intended for ingestion, or “For” (select one of the following, as appropriate: “rectal” or “vaginal”) “use only” [in bold type].

(ii) All applicable warnings listed in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section with the appropriate subheadings highlighted in bold type:

(A) Reye's syndrome warning for drug products containing salicylates set forth in § 201.314(h)(1). This warning

shall follow the subheading "Reye's syndrome:"

(B) Allergic reaction and asthma alert warnings. Allergic reaction warnings set forth in any applicable OTC drug monograph or approved drug application for any product that requires a separate allergy warning. This warning shall follow the subheading "Allergy alert:" The asthma alert warning set forth in §§ 341.76(c)(5) and 341.76(c)(6) of this chapter. This warning shall follow the subheading "Asthma alert:"

(C) Flammability warning, with appropriate flammability signal word(s) (e.g., §§ 341.74(c)(5)(iii), 344.52(c), 358.150(c), and 358.550(c) of this chapter). This warning shall follow a subheading containing the appropriate flammability signal word(s) described in an applicable OTC drug monograph or approved drug application.

(D) Water soluble gums warning set forth in § 201.319. This warning shall follow the subheading "Choking:"

(E) Liver warning set forth in § 201.326(a)(1)(iii) and/or stomach

bleeding warning set forth in § 201.326(a)(2)(iii). The liver warning shall follow the subheading "Liver warning:" and the stomach bleeding warning shall follow the subheading "Stomach bleeding warning:"

(F) Sore throat warning set forth in § 201.315. This warning shall follow the subheading "Sore throat warning:"

(G) Warning for drug products containing sodium phosphates set forth in § 201.307(b)(2)(i) or (b)(2)(ii). This warning shall follow the subheading "Dosage warning:"

(H) Sexually transmitted diseases (STDs) warning for vaginal contraceptive and spermicide drug products containing nonoxynol 9 set forth in § 201.325(b)(2). This warning shall follow the subheading "Sexually transmitted diseases (STDs) alert:"

(iii) "Do not use" [in bold type], followed by all contraindications for use with the product. These contraindications are absolute and are intended for situations in which consumers should not use the product unless a prior diagnosis has been established by a doctor or for situations

in which certain consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted.

(iv) "Ask a doctor before use if you have" [in bold type] or, for products labeled only for use in children under 12 years of age, "Ask a doctor before use if the child has" [in bold type], followed by all warnings for persons with certain preexisting conditions (excluding pregnancy) and all warnings for persons experiencing certain symptoms. The warnings under this heading are those intended only for situations in which consumers should not use the product until a doctor is consulted.

(v) "Ask a doctor or pharmacist before use if you are" [in bold type] or, for products labeled only for use in children under 12 years of age, "Ask a doctor or pharmacist before use if the child is" [in bold type], followed by all drug-drug and drug-food interaction warnings.

(vi) "When using this product" [in bold type], followed by the side effects that the consumer may experience, and the substances (e.g., alcohol) or activities (e.g., operating machinery, driving a car, warnings set forth in § 369.21 of this

chapter for drugs in dispensers pressurized by gaseous propellants) to avoid while using the product.

(vii) "Stop use and ask a doctor if" [in bold type], followed by any signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product. For all OTC drug products under an approved drug application whose packaging does not include a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug product, the following text shall immediately follow the subheading: "[Bullet] side effects occur. You may report side effects to FDA at 1–800–FDA–1088." The telephone number must appear in a minimum 6–point bold letter height or type size.

(viii) Any required warnings in an applicable OTC drug monograph, other OTC drug regulations, or approved drug application that do not fit within one of the categories listed in paragraphs (c)(5)(i) through (c)(5)(vii), (c)(5)(ix), and (c)(5)(x) of this section.

(ix) The pregnancy/breast-feeding warning set forth in § 201.63(a); the third trimester warning set forth in § 201.63(e)

for products containing aspirin or carbaspirin calcium; the third trimester warning set forth in approved drug applications for products containing ketoprofen, naproxen sodium, and ibuprofen (not intended exclusively for use in children).

(x) The "Keep out of reach of children" warning and the accidental overdose/ingestion warning set forth in § 330.1(g) of this chapter.

(6) "Directions", followed by the directions for use described in an applicable OTC drug monograph or approved drug application.

(7) "Other information", followed by additional information that is not included under paragraphs (c)(2) through (c)(6), (c)(8), and (c)(9) of this section, but which is required by or is made optional under an applicable OTC drug monograph, other OTC drug regulation, or is included in the labeling of an approved drug application.

(i) Required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(b), calcium in § 201.70(b), magnesium in § 201.71(b), and potassium in § 201.72(b)) shall appear as follows: "each (insert appropriate dosage unit) contains:" [in bold type (insert

name(s) of ingredient(s) (in alphabetical order) and the quantity of each ingredient). This information shall be the first statement under this heading.

(ii) The phenylalanine/aspartame content required by § 201.21(b), if applicable, shall appear as the next item of information.

(iii) Additional information that is authorized to appear under this heading shall appear as the next item(s) of information. There is no required order for this subsequent information.

(8) "Inactive ingredients", followed by a listing of the established name of each inactive ingredient. If the product is an OTC drug product that is not also a cosmetic product, then the inactive ingredients shall be listed in alphabetical order. If the product is an OTC drug product that is also a cosmetic product, then the inactive ingredients shall be listed as set forth in § 701.3(a) or (f) of this chapter, the names of cosmetic ingredients shall be determined in accordance with § 701.3(c) of this chapter, and the provisions in § 701.3(e), (g), (h), (l), (m), (n), and (o) of this chapter and § 720.8 of this chapter may also apply, as appropriate. If there is a difference in the labeling provisions in this § 201.66 and §§ 701.3 and

720.8 of this chapter, the labeling provisions in this § 201.66 shall be used.

(9) "Questions?" or "Questions or comments?", followed by the telephone number of a source to answer questions about the product. It is recommended that the days of the week and times of the day when a person is available to respond to questions also be included. A graphic of a telephone or telephone receiver may appear before the heading. The telephone number must appear in a minimum 6–point bold type.

(d) Format requirements. The title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(9) of this section shall be presented on OTC drug products in accordance with the following specifications. In the interest of uniformity of presentation, FDA strongly recommends that the Drug Facts labeling be presented using the graphic specifications set forth in appendix A to part 201.

(1) The title "Drug Facts" or "Drug Facts (continued)" shall use uppercase letters for the first letter of the words "Drug" and "Facts." All headings and subheadings in paragraphs (c)(2) through (c)(9) of this section shall use an uppercase letter for the first letter in the first word and lowercase letters for all

other words. The title, headings, and subheadings in paragraphs (c)(1), (c)(2), and (c)(4) through (c)(9) of this section shall be left justified.

(2) The letter height or type size for the title "Drug Facts" shall appear in a type size larger than the largest type size used in the Drug Facts labeling. The letter height or type size for the title "Drug Facts (continued)" shall be no smaller than 8–point type. The letter height or type size for the headings in paragraphs (c)(2) through (c)(9) of this section shall be the larger of either 8–point or greater type, or 2–point sizes greater than the point size of the text. The letter height or type size for the subheadings and all other information described in paragraphs (c)(2) through (c)(9) of this section shall be no smaller than 6–point type.

(3) The title, heading, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section shall be legible and clearly presented, shall have at least 0.5–point leading (i.e., space between two lines of text), and shall not have letters that touch. The type style for the title, headings, subheadings, and all other required information described in paragraphs (c)(2) through (c)(9) of this

section shall be any single, clear, easy-to-read type style, with no more than 39 characters per inch. The title and headings shall be in bold italic, and the subheadings shall be in bold type, except that the word "(continued)" in the title "Drug Facts (continued)" shall be regular type. The type shall be all black or one color printed on a white or other contrasting background, except that the title and the headings may be presented in a single, alternative, contrasting color unless otherwise provided in an approved drug application, OTC drug monograph (e.g., current requirements for bold print in §§ 341.76 and 341.80 of this chapter), or other OTC drug regulation (e.g., the requirement for a box and red letters in § 201.308(c)(1)).

(4) When there is more than one statement, each individual statement listed under the headings and subheadings in paragraphs (c)(4) through (c)(7) of this section shall be preceded by a solid square or solid circle bullet of 5–point type size. Bullets shall be presented in the same shape and color throughout the labeling. The first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems" (i.e., two squares

of the size of the letter "M"). If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the next bulleted statement by at least two square "ems" and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line.

(5) The title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(9) of this section may appear on more than one panel on the outside container of the retail package, or the immediate container label if there is no outside container or wrapper. The continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information. A visual graphic (e.g., an arrow) shall be used to signal the continuation of the Drug Facts labeling to the next adjacent panel.

(6) The heading and information required under paragraph (c)(2) of this section

shall appear immediately adjacent and to the left of the heading and information required under paragraph (c)(3) of this section. The active ingredients and purposes shall be aligned under the appropriate headings such that the heading and information required under paragraph (c)(2) of this section shall be left justified and the heading and information required under paragraph (c)(3) of this section shall be right justified. If the OTC drug product contains more than one active ingredient, the active ingredients shall be listed in alphabetical order. If more than one active ingredient has the same purpose, the purpose need not be repeated for each active ingredient, provided the information is presented in a manner that readily associates each active ingredient with its purpose (i.e., through the use of brackets, dot leaders, or other graphical features). The information described in paragraphs (c)(4) and (c)(6) through (c)(9) of this section may start on the same line as the required headings. None of the information described in paragraph (c)(5) of this section shall appear on the same line as the "Warning" or "Warnings" heading.

(7) Graphical images (e.g., the UPC symbol) and information not described in

paragraphs (c)(1) through (c)(9) of this section shall not appear in or in any way interrupt the required title, headings, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section. Hyphens shall not be used except to punctuate compound words.

(8) The information described in paragraphs (c)(1) through (c)(9) of this section shall be set off in a box or similar enclosure by the use of a barline. A distinctive horizontal barline extending to each end of the "Drug Facts" box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of this section. When a heading listed in paragraphs (c)(2) through (c)(9) of this section appears on a subsequent panel immediately after the "Drug Facts (continued)" title, a horizontal hairline shall follow the title and immediately precede the heading. A horizontal hairline extending within two spaces on either side of the "Drug Facts" box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5) of this section, except the subheadings in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section.

(9) The information set forth in paragraph (c)(6) of this section under the heading "Directions" shall appear in a table format when dosage directions are provided for three or more age groups or populations. The last line of the table may be the horizontal barline immediately preceding the heading of the next section of the labeling.

(10) If the title, headings, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section, printed in accordance with the specifications in paragraphs (d)(1) through (d)(9) of this section, and any other FDA required information for drug products, and, as appropriate, cosmetic products, other than information required to appear on a principle display panel, requires more than 60 percent of the total surface area available to bear labeling, then the Drug Facts labeling shall be printed in accordance with the specifications set forth in paragraphs (d)(10)(i) through (d)(10)(v) of this section. In determining whether more than 60 percent of the total surface area available to bear labeling is required, the indications for use listed under the "Use(s)" heading, as set forth in paragraph (c)(4) of this section, shall be limited to the minimum

required uses reflected in the applicable monograph, as provided in § 330.1(c)(2) of this chapter.

(i) Paragraphs (d)(1), (d)(5), (d)(6), and (d)(7) of this section shall apply.

(ii) Paragraph (d)(2) of this section shall apply except that the letter height or type size for the title "Drug Facts (continued)" shall be no smaller than 7–point type and the headings in paragraphs (c)(2) through (c)(9) of this section shall be the larger of either 7–point or greater type, or 1–point size greater than the point size of the text.

(iii) Paragraph (d)(3) of this section shall apply except that less than 0.5–point leading may be used, provided the ascenders and descenders do not touch.

(iv) Paragraph (d)(4) of this section shall apply except that if more than one bulleted statement is placed on the same horizontal line, the additional bulleted statements may continue to the next line of text, and except that the bullets under each heading or subheading need not be vertically aligned.

(v) Paragraph (d)(8) of this section shall apply except that the box or similar enclosure required in paragraph (d)(8) of this section may be omitted if the Drug Facts labeling is set off from the rest of the labeling by use of color contrast.

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(e) Exemptions and deferrals. FDA on its own initiative or in response to a written request from any manufacturer, packer, or distributor, may exempt or defer, based on the circumstances presented, one or more specific requirements set forth in this section on the basis that the requirement is inapplicable, impracticable, or contrary to public health or safety. Requests for exemptions shall be submitted in three copies in the form of an "Application for Exemption" to the Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The request shall be clearly identified on the envelope as a "Request for Exemption from 21 CFR 201.66 (OTC Labeling Format)" and shall be directed to Docket No. 98N–0337. A separate request shall be submitted for each OTC drug product. Sponsors of a product marketed under an approved drug application shall also submit a single copy of the exemption request to their application. Decisions on exemptions and deferrals will be maintained in a permanent file in

this docket for public review. Exemption and deferral requests shall:

(1) Document why a particular requirement is inapplicable, impracticable, or is contrary to public health or safety; and

(2) Include a representation of the proposed labeling, including any outserts, panel extensions, or other graphical or packaging techniques intended to be used with the product.

(f) Interchangeable terms and connecting terms. The terms listed in § 330.1(i) of this chapter may be used interchangeably in the labeling of OTC drug products, provided such use does not alter the meaning of the labeling that has been established and identified in an applicable OTC drug monograph or by regulation. The terms listed in § 330.1(j) of this chapter may be deleted from the labeling of OTC drug products when the labeling is revised to comply with this section, provided such deletion does not alter the meaning of the labeling that has been established and identified in an applicable OTC drug monograph or by regulation. The terms listed in § 330.1(i) and (j) of this chapter shall not be used to change in any way the specific title, headings, and subheadings required under paragraphs (c)(1) through (c)(9) of this section.

(g) Regulatory action. An OTC drug product that is not in compliance with the format and content

requirements in this section is subject to regulatory action.

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration,
Department of Health and Human Services
Subchapter D. Drugs for Human Use
Part 314. Applications for FDA Approval to
Market a New Drug
Subpart B. Applications

§ 314.150. Content and format of an application.

***

(d) Technical sections. The application is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) of the act to refuse to approve the application. The required technical sections are as follows:

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(5) Clinical data section. A section describing the clinical investigations of the drug, including the following:

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(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration,
Department of Health and Human Services
Subchapter D. Drugs for Human Use
Part 314. Applications for FDA Approval to
Market a New Drug
Subpart B. Applications

§ 314.70 Supplements and other changes to an approved application.

***

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

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(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

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(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this

section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the

drug product(s) made with the manufacturing change.

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