No. SJC-12347

COMMONWEALTH OF MASSACHUSETTS
SUPREME JUDICIAL COURT

BRIAN RAFFERTY,
Plaintiff-Appellant,

v.

MERCK & CO., INC.,
Defendant-Appellee,

and

SIDNEY RUBENSTEIN,
Defendant

ON APPEAL FROM MIDDLESEX COUNTY SUPERIOR COURT

BRIEF OF THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS AMICUS CURIAE IN SUPPORT OF DEFENDANT-APPELLEE MERCK & CO., INC.

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CORPORATE DISCLOSURE STATEMENT

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STATEMENT OF AMICUS CURIAE

The Chamber of Commerce of the United States of America is the largest organization of businesses in the world. It represents 300,000 direct members and represents the interests of more than 3 million companies and professional organizations of all sizes, in every industry, and across all regions of the country.

One of the Chamber's most important responsibilities is representing its members before the courts, legislatures, and executive branches of the States and the federal government. The Chamber regularly files briefs as amicus curiae in litigation that touches on issues of vital concern to the Nation's business community.

The Chamber files this brief to assist the Court in understanding the perspective of the broader business community on the proper standard for imposing tort liability for harm arising from a product. This proceeding may have a widespread, serious impact on product developers in all fields that have until now relied on their understanding of long-

settled principles of tort liability. As the Nation's leading business organization, the Chamber is uniquely positioned to explain the prevailing rule nationwide for imposing liability on a manufacturer only for harm traceable to the manufacturer's own product, and to address the significant policy consequences that might arise from expanding that rule by holding a manufacturer responsible for harms inflicted by its competitors' products.[1]

INTRODUCTION

It is a fundamental and well-settled principle of tort law, both in Massachusetts and across the Nation, that liability for harm caused by products is limited to the persons who actually made or sold

[1] No party or counsel for a party other than amicus, its members, or its counsel authored this brief in whole or in part or made a monetary contribution intended to fund the preparation or submission of this brief. Pursuant to Massachusetts Rule of Appellate Procedure 17 and *Aspinall v. Philip Morris Companies, Inc.*, 442 Mass. 381, 385 n.8 (2004), undersigned counsel state that Williams & Connolly LLP does not represent any of the parties to this case in other litigation presenting the issue presented in this case. Undersigned counsel further state that Williams & Connolly LLP has represented and represents defendant-appellee Merck & Co., Inc., in other cases, though not in connection with the issue presented in this case.

the injurious products. That principle applies regardless of the theory of liability upon which a plaintiff proceeds. A manufacturer thus has no duty to warn consumers about products made and sold by a competitor, and it cannot be held liable for injuries caused by its competitor's products when the manufacturer does not control the manufacture of the products and has made no representations about those products.

That longstanding principle of tort liability applies with equal force in the pharmaceutical industry, as courts around the country have confirmed. More than a hundred state and federal courts to have considered the questions presented here have concluded that pharmaceutical manufacturers, like all other manufacturers, may be held liable only for harm caused by their own products. There is no reason to carve out an exception for the pharmaceutical industry and send Massachusetts down the path toward eroding basic tort doctrines and disturbing settled expectations about the scope of tort liability.

Creating an exception to ordinarily applicable tort principles in the pharmaceutical context would lead to undesirable policy outcomes. The cost of innovation would inevitably increase, and investment in developing and marketing innovative products would inevitably decrease—harming the economy and, uniquely in this field, public health. The Court should not tamper with prevailing tort principles and risk such profound problems for industrial and pharmaceutical innovation.

ARGUMENT

I. FUNDAMENTAL PRINCIPLES OF TORT LAW PRECLUDE THE IMPOSITION OF LIABILITY ON A MANUFACTURER FOR HARM CAUSED BY PRODUCTS MANUFACTURED BY ANOTHER

The American business community organizes its activities across the country in reliance on certain universally applicable rules of tort law. One of those rules is the venerable principle that a manufacturer can be held liable only for harms caused by products it actually made or sold. That principle, and others like it, provide a backstop on which manufacturers and other businesses depend. No matter the theory of liability, under any set of facts, liability does not exist unless a specific product

links the allegedly culpable manufacturer to a particular injury. No such link exists when a plaintiff is injured by a product the defendant manufacturer did not make and about which it has not made any representations. To impose liability without such a link would upend the settled expectations of businesses of all kinds throughout the country and introduce serious uncertainty and instability into tort law.

As this Court has long held, "[a] manufacturer of *a product* has a duty to warn foreseeable users of dangers in the use of *that product* of which he knows or should have known." *Mitchell* v. *Sky Climber, Inc.*, 396 Mass. 629, 631 (1986) (emphases added). That duty—"[t]he duty of the manufacturer to warn of the dangers in the use of *his product*"—is "well established." *Wolfe* v. *Ford Motor Co.*, 6 Mass. App. Ct. 346, 349 (1978) (emphasis added). And the duty requires a manufacturer of a product to "exercise reasonable care to prevent injury to those persons who it is foreseeable will come in contact with, and consequently be endangered by, *that product*." *H. P. Hood & Sons, Inc.* v. *Ford*

Motor Co., 370 Mass. 69, 75 (1976) (emphasis added). What the District Court for the District of Massachusetts only a few months ago termed this "long-settled principle", *In re Zofran (Ondansetron) Product Liability Litigation*, MDL No. 15-2657, 2017 WL 3448548, at *4 (D. Mass. Aug. 4, 2017), has been stated time and again in Massachusetts in a line of cases stretching over decades. *See, e.g.*, *Morin* v. *AutoZone Northeast, Inc.*, 79 Mass. App. Ct. 39, 51 (2011)*; Farley* v. *Edward E. Tower & Co.*, 271 Mass. 230, 233 (1930).

Plaintiff seeks to restate or narrow the decades of Massachusetts decisions foreclosing his theory of liability. For example, plaintiff notes that, over 70 years ago, this Court held that failure-to-warn liability could attach even absent a *business* relationship between the parties. Br. 8 (citing *Carter* v. *Yardley & Co.*, 319 Mass. 92, 96-97 (1946)). As a result, plaintiff argues, defendants can also be held liable when no link at all connects the plaintiff's harm to the defendant's alleged omission. *Id.* But plaintiff ignores that, in the very same case, this Court made clear that

the duty to warn arises only when "a manufacturer . . . owning or controlling *a thing* . . . deals with or disposes of *that thing* in a way that . . . will probably carry *that thing* into contact with some person . . . who will probably be ignorant of the danger." *Carter*, 319 Mass. at 96 (emphases added). As this Court put it elsewhere, it is when "*an instrumentality*" links a manufacturer with a person unknowingly imperiled by "*that thing*" that the manufacturer acquires the responsibility to reasonably warn of the threat. *Mann* v. *Cook*, 346 Mass. 174, 176–77 (1963) (citing *Carter*, 319 Mass. at 96) (emphases added).

The law of Massachusetts is no outlier in this regard. To the contrary, the vast majority of States agree that a manufacturer is responsible to warn only those who use its own products, not those who use products made and sold by its competitors. "[G]eneral tort principles" do not "impose liability with respect to a defendant that did not sell, distribute, manufacture, or otherwise have contact with the allegedly harmful product." *Schrock* v. *Wyeth, Inc.*, 727 F.3d 1273, 1284 (10th Cir. 2013). Absent

the link of a common "instrumentality" leading from the defendant to the plaintiff, *Mann*, 346 Mass. at 176–77, defendants would pay for harms they did not cause, severing the essential connection that justifies imposing liability in the first place.

The rule that a manufacturer is responsible to warn only those who use its own products—which the First Circuit, discussing Massachusetts law, called a matter of "classical tort principle," *Carrier* v. *Riddell, Inc.*, 721 F.2d 867, 868 (1983)—is also codified in Section 388 of the Second Restatement of Torts and its comments, on which this Court and lower Massachusetts courts have routinely relied to clarify the scope of the duty to warn. *See Schaeffer* v. *General Motors Corp.*, 372 Mass. 171, 174 (1977) (citing Restatement (Second) of Torts § 388 (1977)); *Mann*, 346 Mass. at 177 (same); *Fiorentino* v. *A. E. Staley Manufacturing Co.*, 11 Mass. App. Ct. 428, 433 (1981) (same); *Wolfe*, 6 Mass. App. Ct. at 350 (same).

Section 388 of the Second Restatement provides that "those who supply chattels have a duty to warn 'those whom the supplier expects to use the chattel . . . or to be endangered by its probable use.'"

Carrier, 721 F.2d at 869 (alteration in original) (quoting Restatement (Second) of Torts § 388). And comment (e) to that section adds that liability "'exists only if physical harm is caused by the use of the chattel by those for whose use the chattel is supplied.'" *Id.* The Third Restatement of Torts makes the same point even more clearly: liability for failure to warn of a risk from the use of a product attaches "'when the foreseeable risks of harm posed by *the product* could have been reduced or avoided by the provision of reasonable instructions or warnings . . . and the omission of the instructions or warnings renders *the product* not reasonably safe.'" *Vassallo* v. *Baxter Healthcare Corp.*, 428 Mass. 1, 21 (1998) (alteration in original) (quoting Restatement (Third) of Torts, Products Liability § 2(c) (1998)) (emphases added)).

The foregoing rule, moreover, applies whatever the theory of liability. Whether a plaintiff frames the claim in terms of fraud, strict liability, or something in between, tort law always requires a link between the plaintiff's harm and the defend-

ant's act or statement. Plaintiff insists otherwise, arguing that this case is different because his alleged harm arose not from Merck's product but from its representations *about* the product. Br. 14-15, 17-18, 21. But he ignores the principle that, in Massachusetts as elsewhere, "[a] manufacturer has the duty to caution *purchasers of its product* by way of adequate warnings of foreseeable latent dangers involved in *the product's* normal and intended use." *Fiorentino*, 11 Mass. App. Ct. at 433 (emphases added). Merck had no duty to warn plaintiff, who did not use Merck's product, because Merck never made any representations to him. The warnings it did issue were directed only at the users of its own product. Neither Massachusetts law nor the general principles of tort law Massachusetts has adopted require anything else.

Plaintiff seeks to shelter behind outlying decisions from other States that have created a new duty for manufacturers to warn consumers who were injured by the products of the manufacturers' competitors. But those cases merely illustrate that,

in States which have adopted tort principles different from those in Massachusetts, courts have followed those divergent principles to reach conclusions that Massachusetts law forbids. For example, in *Conte* v. *Wyeth, Inc.*, 168 Cal. App. 4th 89, 103-104 (Cal. Ct. App. 2008), a California intermediate court observed that, under California law, "misrepresentations that implicate a risk of physical harm to others" are governed by the rules set forth in Section 311 of the Second Restatement of Torts. *Id.* at 103-104. This Court, by contrast, has made clear that the tort Section 311 codifies "is not, at this time, a recognized cause of action in Massachusetts." *Gianocostas* v. *Interface Group Massachusetts, Inc.*, 450 Mass. 715, 727–28 (2008). Plaintiff therefore cannot rely on the duty *Conte* recognized.

Similarly, in *Kellogg* v. *Wyeth*, 762 F. Supp. 2d 694 (D. Vt. 2010), a federal district court in Vermont, relying on *Conte*, concluded that "the common law as it has developed in Vermont" extended a brand-name drug manufacturer's duty to warn to cover those injured by its competitor's products. *Id.* at 708.

Even if that court got Vermont law right, however, the "common law as it has developed in" Massachusetts requires a different conclusion here.

Where, as here, the plaintiff was injured by a product made by a competitor, no common "instrumentality" exists linking the manufacturer's acts and statements with the plaintiff's injury. *See Mann*, 346 Mass. at 176–77. It would "stretch . . . foreseeability" far beyond that concept's capacity if a brand-name drug manufacturer faced liability for harm even when the harm giving rise to liability was actually caused by a competing version of the manufacturer's product. *Foster* v. *American Home Products Corp.*, 29 F.3d 165, 171 (4th Cir. 1994).

In sum, it is immaterial whether a plaintiff, injured by a product, asserts a claim arising in fraud, negligence, or strict liability. If the defendant manufacturer did not produce that product or make representations about it, then the manufacturer cannot be liable. Nor does the outcome change if the plaintiff argues that he or she was harmed by the defendant's statements about its own product (a product the plaintiff never used), as opposed to

statements about the product that actually inflicted the plaintiff's injury. Under fundamental rules governing tort disputes—rules that Massachusetts law incorporates and applies—only the producer or seller of a product, or one who makes representations about that product, should be held responsible for harm the product inflicts.

II. THERE IS NO VALID JUSTIFICATION TO CREATE AN EXCEPTION TO FUNDAMENTAL PRINCIPLES OF TORT LAW IN THE CONTEXT OF THE PHARMACEUTICAL INDUSTRY

The foregoing basic principles of tort law apply across all industries, and there is no reason to carve out an exception to those principles solely for pharmaceutical manufacturers. Courts across the Nation have overwhelmingly held that pharmaceutical manufacturers are not liable for injuries caused by their competitors' products. In the absence of an instrumentality linking a defendant's product or statements to the plaintiff's injuries, those courts—including every federal court of appeals to consider the question and state courts in more than a dozen jurisdictions—have concluded that such a defendant cannot be considered to have caused the

plaintiff's injuries or to have a duty to warn against them.

Contrary to plaintiff's contention (Br. 21), there is nothing "unique" to this case or any of the other cases presenting the same question that have been decided over the last two decades. Instead, this case requires nothing more than application of the well-established principles that govern every tort case. Under those principles, the answer is clear: a manufacturer may be called to account only for the harms its own products inflict, regardless of the theory of liability on which the plaintiff's claim is based.

A. By way of background, a pharmaceutical manufacturer seeking regulatory approval from the Food and Drug Administration (FDA) for a new drug must submit a new drug application (NDA), showing that the drug is safe for use and effective for its indications and that the proposed label accurately and sufficiently describes the risks of its use. *See* 21 U.S.C. § 355(b)(1), (d). Once granted, an NDA brings with it certain responsibilities, including

the obligation to submit annual reports demonstrating the safety, effectiveness, and appropriate labeling of approved drugs. *See* 21 C.F.R. §§ 314.80, 314.81. Pharmaceutical manufacturers that hold NDAs may also submit supplemental applications to change the label and accompanying warnings of a drug; they are required to do so if they learn of a risk not already adequately identified. *See* 21 C.F.R. §§ 314.70, 314.71.

A pharmaceutical manufacturer may sell an NDA to another company, transferring ownership of the right to make the drug as well as the attendant regulatory obligations. *See* 21 C.F.R. § 314.72. Thereafter, the new NDA holder has exclusive authority to revise the label and submit supplemental applications regarding label changes, and it has the exclusive responsibility to monitor the market and submit annual reports and supplemental applications to FDA. *See* 21 C.F.R. §§ 314.70, 314.71.

Congress has also created a streamlined process for approval of generic versions of brand-name drugs once the patent exclusivity accorded to new pharma-

ceutical products expires. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (Hatch-Waxman Act) (codified as amended at 21 U.S.C. § 355(j)). A generic pharmaceutical manufacturer can submit an abbreviated new drug application (ANDA), which requires only that the manufacturer show its product is "bioequivalent" to the brand-name drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv). That process allows the generic manufacturer to rely on the safety and effectiveness studies conducted by the original brand-name manufacturer at its own expense. *See id.* After ANDA approval, a generic manufacturer is required to maintain a label and accompanying warnings for its product that are "the same" as those used for the brand-name drug with which the generic version competes. *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 613 (2011) (citing 21 U.S.C. § 355(j)(2)(A)(v), 355(j)(4)(G), and 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7)).

While generic pharmaceutical manufacturers are not authorized independently to update the labels for their products, *Mensing*, 564 U.S. at 613, they

otherwise have similar responsibilities to those of NDA holders: they are also required to monitor the market and to submit annual reports and supplemental applications (when appropriate) to FDA. *See* 21 C.F.R. §§ 314.70, 314.71, 314.80, 314.81, 314.97, 314.98; Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992).

B. Since 1996, at least 134 federal and state decisions have concluded that pharmaceutical manufacturers cannot be held liable for products made and sold by others. Those decisions from "[t]he overwhelming majority of courts," *Zofran*, 2017 WL 3448548, at *6, rely on three basic lines of reasoning. *First*, general principles of tort law impose liability on manufacturers only for injuries caused by their own products, and do not impose a duty on manufacturers to warn consumers about the risks associated with other manufacturers' products. *Second*, the labels and warnings issued by brand-name manufacturers are representations only about the safety of their own products, not about the safety of their competitors' products. *Third*, policy considerations—and in particular the need to promote

innovation—strongly counsel against creating a special rule for pharmaceutical manufacturers for injuries resulting from their competitors' products.

The first federal court of appeals to confront this question was the Fourth Circuit, in a 1994 case on whether a plaintiff injured by taking the generic version of a drug could recover for his injuries from the manufacturer of the drug's brand-name analogue. *See Foster*, 29 F.3d at 168-169. The Fourth Circuit held that the brand-name manufacturer could not be held liable. *See id.* at 169. The court reasoned that each manufacturer was responsible for preventing the consumers of its own products from being injured, and correspondingly liable only for its own products' harms; it "stretch[ed] the concept of foreseeability too far" to require brand-name manufacturers to take responsibility for harm that befell those who never used their products. *See id.* at 169-171.

Since *Foster*, six other federal courts of appeals have likewise held that brand-name pharmaceutical manufacturers cannot face liability for injuries caused by their competitors' products. For

example, the Eighth Circuit held, in an opinion reinstated after reversal on other grounds by the Supreme Court, that a plaintiff could not adequately show that the brand-name manufacturers "owed her a duty of care necessary to trigger liability" under Minnesota law, in part because their statements about their products were representations made to "*their* customers, not the customers of their competitors." *Mensing* v. *Wyeth, Inc.*, 588 F.3d 603, 613 n.9, 614 (2009) (emphasis added), *rev'd*, 564 U.S. 604 (2011), *opinion reinstated in relevant part*, 658 F.3d 867 (8th Cir. 2011).

The Sixth Circuit followed suit, applying Kentucky law to "reject the argument that a name-brand drug manufacturer owes a duty of care to individuals who have never taken the drug actually manufactured by that company." *Smith* v. *Wyeth, Inc.*, 657 F.3d 420, 424 (2011). Several years later, the Sixth Circuit revisited the issue in a multidistrict litigation, examining the law of some 22 States and concluding in each case either that a manufacturer owed no duty to a plaintiff injured by a drug produced by its competitor, or that the plaintiff's

suit was otherwise barred under state-specific product-liability statutes or rules. *See In re Darvocet, Darvon & Propoxyphene Products Liability Litigation*, 756 F.3d 917, 937-939, 941-954 (2014).

The Fifth, Ninth, Tenth, and Eleventh Circuits have also held that a plaintiff has a claim only against the manufacturer of the pharmaceutical product that caused the injury, no matter the theory of liability. *See Lashley* v. *Pfizer, Inc.*, 750 F.3d 470, 476 (5th Cir. 2014) (per curiam) (concluding that, "because [a]ppellants did not ingest the brand manufacturers' products, these defendants have no common-law duty to them"); *Moretti* v. *Wyeth, Inc.*, 579 Fed. Appx. 563, 565 (9th Cir. 2014) (holding that "Nevada law [does not] recognize[] a claim against the [b]rand [d]efendants for misrepresentation"), cert. denied, 135 S. Ct. 1398 (2015); *Guarino* v. *Wyeth, LLC*, 719 F.3d 1245, 1253 (11th Cir. 2013) (concluding that "Florida law does not recognize a [misrepresentation] claim against the brand manufacturer of a prescription drug when the plaintiff is known to have consumed only the generic form"); *Schrock*, 727 F.3d at 1283-1286 (noting that

"[n]o authority is cited to suggest that a manufacturer may be held liable under Oklahoma law for concealing a defect in a product that is never purchased or used by the plaintiff"); *see also Zofran*, 2017 WL 3448548, at *16 (noting the "overwhelming and well-reasoned majority view, which has been set out in multiple opinions by a variety of federal and state courts").

In all of these cases, the courts, while applying the law of different States, reached the same conclusion. Though there are certain variations in tort law from State to State, the law of each State grows out of and incorporates certain common principles. One of those principles is that a defendant can be held liable only for harm fairly traceable to its own acts or omissions. In the product-liability context, an individual manufacturer can thus be called to account only for harms caused by its own products. Courts have consistently concluded that manufacturers cannot be held responsible for failing to warn against or prevent harm caused by products they did not make, from which they did not

profit, and about which they made no statements at all.[2]

As in other similarly situated cases, plaintiff here argues that, in the wake of *Mensing* and *Wyeth* v. *Levine*, 555 U.S. 555 (2009), the law anomalously treats brand-name and generic pharmaceutical manufacturers differently: under *Levine*, consumers injured by brand-name pharmaceutical drugs may sue brand-name manufacturers for their harms, while under *Mensing*, generic manufacturers are not liable for injuries their products inflict. Br. 23-25. But the mere fact of this inconsistency in *federal* preemption law does not justify reshaping the accepted principles of *state* tort liability and discarding principles that guide the decisionmaking of manufacturers in all industries. "As always, Congress and FDA retain the authority to change the law and regulations if they so desire," and resolving

[2] Only *Wyeth* v. *Weeks*, 159 So. 3d 649, 670, 672 (Ala. 2014), threatened to reshape the settled understanding on the question presented here. But *Weeks* was promptly repudiated by the Alabama legislature, which enacted a statutory prohibition on holding a defendant liable for harms caused by any product it had not "designed, manufactured, sold, or leased." Ala. Code § 6-5-530(a) (2017).

inconsistencies such as this one is the proper province of those federal actors. *Mensing*, 564 U.S. at 626.[3] That is particularly true in a case like this, where the choice of liability rule implicates "health care policy for the [entire] country." Victor E. Schwartz et al., *Warning: Shifting Liability to Manufacturers of Brand-Name Medicines When the Harm Was Allegedly Caused by Generic Drugs Has Severe Side Effects*, 81 Fordham L. Rev. 1835, 1875 (2013) (Schwartz). This "complex set of questions at the intersection of federal drug regulation and state tort law," requiring "a balancing of multiple considerations of law and policy," "should be left to the political branches, whether at the state or federal level." *Zofran*, 2017 WL 3448548, at *16.

[3] As the Superior Court noted, *see.* R.A. 157, FDA has already twice issued proposed rules for public comment which could restore generic pharmaceutical manufacturer liability for harms caused by their own products. *See Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*, 80 Fed. Reg. 8577-01 (Feb. 18, 2015); *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*, 78 Fed. Reg. 67985-02 (Nov. 13, 2013).

It would create more problems than it would solve if longstanding fundamental principles of tort law were modified to address potentially temporary anomalies in federal preemption law. That is especially true because the question of whether to expand tort liability to those that did not manufacture the injury-causing product "involves policy choices . . . more appropriately within the legislative domain." *Huck* v. *Wyeth, Inc.*, 850 N.W.2d 353, 376 (Iowa 2014) (internal quotation marks omitted), *cert. denied*, 135 S. Ct. 1699 (2015). And any exception this Court sought to carve into fundamental tort principles, even if intended to apply only to the pharmaceutical industry, would introduce uncertainty across all industries in the calculation of what tort liability an innovator should expect to face. The Court should not accept the invitation to create a far-reaching solution to a potentially temporary problem when that solution risks significant costs to the public and the economy by discouraging innovation.

III. CREATING AN EXCEPTION TO FUNDAMENTAL PRINCIPLES OF TORT LAW IN THE CONTEXT OF THE PHARMACEUTICAL INDUSTRY WOULD HAVE SERIOUS ADVERSE POLICY CONSEQUENCES

This Court has explained that it will determine whether a defendant owed a duty of care to a particular plaintiff "by reference to existing social values and customs and appropriate social policy." *Coombes* v. *Florio*, 450 Mass. 182, 187 (2007) (Ireland, J. concurring) (internal quotation marks omitted); *id.* at 197 (Greaney, J., concurring in part and dissenting in part) (same); *id.* at 206 (Cordy, J., dissenting) (same). Courts across the Nation have recognized that public-policy considerations strongly support the conclusion that fundamental principles of tort law forbid imposing liability on a manufacturer for harm caused by its competitors' products. Shifting liability onto innovative manufacturers in any industry comes at too high a cost and risks too much.

The original developer of a product incurs significant costs. And no matter how costly its development, a new product may never even be sold,

much less prove successful, if regulatory or marketplace obstacles prove insuperable. Even if the developer manages to steer a product to the marketplace and market it successfully, it has no guarantee that its profits will ever cover its investment. And of course, the developer must also consider, and price in, the potential cost of liability to consumers for the product. The challenges a developer faces are all the more significant given the competition of alternatives, which can crowd the original developer out of the market entirely—even more so when competitors can entirely forgo the cost of development, regulatory approval, and marketing.

As many courts have recognized, those challenges are uniquely acute for pharmaceutical manufacturers. *See Kelly* v. *Wyeth*, No. Civ.A.MICV200303314B, 2005 WL 4056740, at *4 (Mass. Super. Ct. May 6, 2005). Though "[p]ublic policy favors the development and marketing of new and more efficacious drugs," *Payton* v. *Abbott Labs*, 386 Mass. 540, 573 (1982), developing and obtaining approval for groundbreaking pharmaceutical products can require enormous investment over decades. And federal

law and regulations are especially solicitous toward competing generic versions which, after the brand-name manufacturer's period of exclusivity expires, almost invariably capture most of the product's market. But similar problems "may arise with other types of consumer goods, ranging from nonprescription drugs and foods to household chemicals and appliances; in other words, crossover tort litigation could occur in any market served by brand-name companies that actively promote their wares but face competition from largely identical but lower-priced store brands" or other competing alternatives. Lars Noah, *Adding Insult to Injury: Paying for Harms Caused by a Competitor's Copycat Product*, 45 Tort Trial & Ins. Prac. L.J. 673, 694 (Spring-Summer 2010).

"A fair and rational system of tort liability must balance a variety of different factors, including not only providing compensation for injured persons, but also such factors as the appropriate allocation of risk." *Zofran*, 2017 WL 3448548, at *14. Whatever the challenges of developing new products, developers have always been able to rely on the

settled understanding that their exposure to risk is limited to the products they manufacture or sell themselves. That settled understanding allows manufacturers to anticipate their potential liability based on their sales; to set the price of their products at a level adequate to cover those projected costs; and to negotiate with insurers to cover that projected liability. Developers depend on that understanding when they make decisions about how to develop new products. And relying on that understanding, American industry has achieved dazzling success in innovation in all fields, with appropriate opportunity for those injured by innovative products to recover from those that produced them. *See Huck*, 850 N.W.2d at 379-380. At the same time, by placing liability solely on the actual manufacturer of a product, this rule sharpens manufacturers' incentives to ensure that their products are safe and bear adequate warnings, and underscores for consumers that a product's manufacturer is the authoritative source of warning information for that product.

Shifting the cost of harm to consumers onto manufacturers whose products the consumers did not even use risks permanently disrupting developers' ability to plan for the future and to project the size of their risk. Developers of new products would face liability arising from product sales made not by them but by their competitors, which took advantage of the innovators' initial investment in research, regulatory approval, and marketing. Such a shift would effectively force innovators in all industries to serve as insurers for the tort liability arising from all sales of their own and their competitors' products, increasing their cost but not the cost of competing alternatives—a particularly unjust result where the competitors were able to bring their products to market without paying for development, regulatory approval, or marketing. *See, e.g.*, Sarah C. Duncan, Note, *Allocating Liability for Deficient Warnings on Generic Drugs: A Prescription for Change*, 13 Vand. J. Ent. & Tech. L. 185, 215 (2010); Schwartz 1861.

What is more, the assignment of tort liability to manufacturers for products they do not make would

expose product developers to risk based on sales activity and regulatory compliance they could neither control nor monitor, introducing lasting, unavoidable uncertainty into the calculus of product development. A manufacturer inevitably must, and should, consider tort liability to consumers of its products. But the new rule plaintiff asks this Court to adopt here would not merely multiply the size of tort liability; it would also render it unpredictable. The loss of predictability in projecting risk is even costlier than the dollar value of tort judgments in favor of the class of consumers injured by competitors' products. *See* Schwartz 1870. And manufacturers would also face significant planning and compliance costs from the need to balance this new rule, applicable in Massachusetts, with the long-settled rule that would still apply throughout the rest of the Nation.

As this Court has observed of a different form of unjustifiably extended manufacturer liability, there can be no doubt that the "[i]mposition of such broad liability could have a deleterious effect on the development and marketing of new" innovative

products of all kinds, pharmaceutical and otherwise. *Payton*, 386 Mass. at 573–74. *First*, the cost of innovative products would necessarily rise to fund the increased scope of liability that would follow once competing versions entered the market. That would have particularly grave consequences in the context of the pharmaceutical industry, where higher prices could have an effect on public health. *See, e.g.*, *Darvocet*, 756 F.3d at 944, 945, 947, 948-949; Teresa Moran Schwartz, *Prescription Products and the Proposed Restatement (Third)*, 61 Tenn. L. Rev. 1357, 1360 & nn.17-18 (1994) (T. Schwartz).

Second, confronted with ballooning and unpredictable liability costs, manufacturers would necessarily devote fewer resources to innovation and release fewer innovative new products. *See*, *e.g.*, *Darvocet*, 756 F.3d at 944, 945, 947, 948-949; T. Schwartz 1360 & nn.17-18. Manufacturers would have less incentive to launch new products because their profits from those products would be decreased (or wiped out altogether) by the murky and expanded scope of their tort exposure.

Innovative developers would now have to guess not merely at the size of their own liability, but also at the cost of insuring the sales of the product for an unknown period into the future. Any company contemplating investing in innovative research and development would have to weigh the benefits of new products against enormous risks it could neither calculate nor control. This unpredictability would also affect the ability of manufacturers to arrive at meaningful valuations of their product lines and businesses as a whole, hampering their access to credit and their ability to sell, and license, their own products and product lines.

"[I]t is unclear what the impact of such a potentially enormous shift in liability may have on the development of new drugs" and other products. *Zofran*, 2017 WL 3448548, at *14. Perhaps only blockbuster products, promising large and lasting profits, would prove worth the candle. Or perhaps manufacturers would eliminate development lines and product categories altogether, producing a smaller number of products in order to control their potential liability. No matter the specific strategy

adopted by individual manufacturers, the aggregate consequence is clear and un-avoidable: consumers would see fewer new products brought to market. *See* Schwartz 1871.

For most types of products, that decline might simply represent overall losses to the economy. For the pharmaceutical industry, however, the prospect is much more serious: public health as a whole would suffer as overbroad liability necessarily "[d]iminish[ed] the chances of significant independent manufacturer-sponsored research and development of new biologics." *Payton*, 386 Mass. at 573 n.17 (emphasis omitted) (quoting *Hearing Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare*, 94th Cong., 2d Sess. 119 (Sept. 23, 1976) (statement of Assistant Surgeon General David Sencer)); *see also* H. William Smith III, Note, *Vaccinating AIDS Vaccine Manufacturers Against Product Liability*, 42 Case W. Res. L. Rev. 207, 218 & n.80 (1992) (discussing the efforts of courts in other States to shape the liability of pharmaceutical manufacturers to avoid the risk of "deter[ring] the

marketing of new products for fear of large adverse monetary judgments").

The foregoing policy considerations have long informed the fundamental rule that tort liability can attach only where a common instrumentality links the injured person to the alleged wrongdoer. A more expansive liability regime would disturb the existing equilibrium between the undoubted obligation to redress injuries and the need to allocate liability in a way that maximizes innovation and overall well-being. This Court should not disregard those policy considerations by creating an exception to well-settled tort principles for pharmaceutical manufacturers.

Nor is there any valid reason to believe that such an exception could remain cabined to the pharmaceutical industry. As another state court of last resort has noted, creating such an exception would leave courts on a "slippery slope." *Huck*, 850 N.W.2d at 380. "If a car seat manufacturer recognized as the industry leader designed a popular car seat, could it be sued for injuries sustained by a con-

sumer using a competitor's seat that copied the design?" *Id.*; *see also* Schwartz 1869-1870 (noting that "there is no principle limiting competitor liability to prescription drugs"). At a minimum, a new rule of tort liability for the pharmaceutical industry would destabilize the assumptions made by manufacturers in other industries about how far tort liability can run, and prudent manufacturers in all industries would have to consider the possibility that such a rule would be applied to their products as well.

The dramatic change to tort law that plaintiff is seeking in this case threatens serious and unmistakable consequences. This Court should not adopt a rule that would disrupt the process of developing new products in any industry, much less the process of developing life-saving pharmaceuticals.

CONCLUSION

The judgment of the Superior Court should be affirmed.

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ADDENDUNDUM OF STATUTES AND REGULATIONS

21 U.S.C. § 355: New Drugs

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with

representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

* * *

(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.

* * *

(j) Abbreviated new drug applications

. . .

(2)(A) An abbreviated application for a new drug shall contain—

. . .

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

. . .

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—

. . .

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

Ala. Code § 6-5-530

(a) In any civil action for personal injury, death, or property damage caused by a product, regardless of the type of claims alleged or the theory of liability asserted, the plaintiff must prove, among other elements, that the defendant designed, manufactured, sold, or leased the particular product the use of which is alleged to have caused the injury on which the claim is based, and not a similar or equivalent product. Designers, manufacturers, sellers, or lessors of products not identified as having been used, ingested, or encountered by an allegedly injured party may not be held liable for any alleged injury. A person, firm, corporation, association, partnership, or other legal or business entity whose design is copied or otherwise used by a manufacturer without the designer's express authorization is not subject to liability for personal injury, death, or property damage caused by the manufacturer's product, even if use of the design is foreseeable.

(b) This section is not intended in any way to alter or affect any other principle of law, including those that apply under the Alabama Medical Liability Act, Section 6-5-540 et seq. ; those that apply to successor entities, distributors, component manufacturers, or manufacturers who use component parts in assembling products for sale as complete units; or those that apply to the operation of a contract, including a licensing agreement.

21 C.F.R. § 314.70: Supplements and other changes to an approved NDA

(a) Changes to an approved NDA. (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved NDA;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in 201.57(a)(15) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an NDA that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that NDA.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes). (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement--Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement--Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(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 NDA 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:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(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 NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

(d) Changes to be described in an annual report (minor changes). (1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the NDA or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the NDA;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved NDA, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(1) and (2) of this section.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved NDA that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) Protocols. An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved NDA, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) Patent information. The applicant must comply with the patent information requirements under section 505(c)(2) of the Federal Food, Drug, and Cosmetic Act and 314.53.

(g) Claimed exclusivity. If an applicant claims exclusivity under 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under 314.50(j).

(h) Different drug. An applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application. For purposes of this paragraph (h), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (h), an applicant may supplement the 505(b)(2) application to seek approval of a different strength.

21 C.F.R. § 314.71: Procedures for submission of a supplement to an approved application

(a) Only the applicant may submit a supplement to an application.

(b) All procedures and actions that apply to an application under 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements except as specified otherwise in this part.

21 C.F.R. § 314.72: Change in ownership of an application

(a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:

(1) The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.

(2) The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:

(i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;

(ii) The date that the change in ownership is effective; and

(iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under 314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in 20.45 of FDA's public information regulations.

(b) The new owner shall advise FDA about any change in the conditions in the approved application under 314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

21 C.F.R. § 314.80: Postmarketing reporting of adverse drug experiences

(a) Definitions. The following definitions of terms apply to this section:

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Individual case safety report (ICSR). A description of an adverse drug experience related to an individual patient or subject.

ICSR attachments. Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e. , it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital

anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e. , included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of adverse drug experiences. Each applicant having an approved application under 314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including

information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (g)(2) of this section, these reports must be submitted to the Agency in electronic format as described in paragraph (g)(1) of this section.

(1)(i) Postmarketing 15-day "Alert reports". The applicant must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant.

(ii) Postmarketing 15-day "Alert reports"--followup. The applicant must promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this

section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor (nonapplicant). To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the nonapplicant, and the applicant must then comply with the requirements of this section. Under this circumstance, the nonapplicant must maintain a record of this action which must include:

(A) A copy of each adverse drug experience report;

(B) The date the report was received by the nonapplicant;

(C) The date the report was submitted to the applicant; and

(D) The name and address of the applicant.

(2) Periodic adverse drug experience reports. (i) The applicant must report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant must submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may

extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain:

(A) Descriptive information. (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated); and

(4) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs submitted under paragraph (c)(2)(ii)(B) of this section.

(B) ICSRs for serious, expected, and nonserious adverse drug experiences. An ICSR for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse drug experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to

adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) Scientific literature. A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (i.e. , serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(e) Postmarketing studies. An applicant is not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(f) Information reported on ICSRs. ICSRs include the following information:

(1) Patient information.

(i) Patient identification code;

(ii) Patient age at the time of adverse drug experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) Adverse drug experience.

(i) Outcome attributed to adverse drug experience;

(ii) Date of adverse drug experience;

(iii) Date of ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect medical product(s).

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a prescription or nonprescription product;

(vi) Whether the product is a combination product as defined in 3.2(e) of this chapter;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) Initial reporter information.

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) Applicant information.

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day "Alert report";

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(g) Electronic format for submissions. (1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (g)(1) of this section.

(h) Multiple reports. An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(i) Patient privacy. An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(j) Recordkeeping. The applicant must maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(l) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does

not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term "applicant" also includes any person reporting under paragraph (c)(1)(iii) of this section.

21 C.F.R. § 314.81: Other postmarketing reports

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) NDA--Field alert report. The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA--Field Alert Report."

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or

otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(ii)(a) Distribution data. Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(b) Authorized generic drugs. If applicable, the date each authorized generic drug (as defined in 314.3) entered the market, the date each authorized generic drug ceased being distributed, and the corresponding trade or brand name. Each dosage form and/or strength is a different authorized generic drug and should be listed

separately. The first annual report submitted on or after January 25, 2010 must include the information listed in this paragraph for any authorized generic drug that was marketed during the time period covered by an annual report submitted after January 1, 1999. If information is included in the annual report with respect to any authorized generic drug, a copy of that portion of the annual report must be sent to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drug Quality Assessment, Bldg. 21, rm. 2562, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, and marked "Authorized Generic Submission" or, by e-mail, to the Authorized Generics electronic mailbox at AuthorizedGenerics@fda.hhs.gov with "Authorized Generic Submission" indicated in the subject line. However, at such time that FDA has required that annual reports be submitted in an electronic format, the information required by this paragraph must be submitted as part of the annual report, in the electronic format specified for submission of annual reports at that time, and not as a separate submission under the preceding sentence in this paragraph.

(iii) Labeling. (a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under 201.100(d)(3) of this chapter (i.e. , the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of 11.10(a), (c) through (h),

and (k), and the corresponding requirements of 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv) Chemistry, manufacturing, and controls changes. (a) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(b) A full description of the manufacturing and controls changes not requiring a supplemental application under 314.70 (b) and (c), listed by date in the order in which they were implemented.

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data. (a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles,

papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) Status reports of postmarketing study commitments. A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under 201.23 of this chapter. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(a) Content of status report. The following information must be provided for each postmarketing study reported under this paragraph:

(1) Applicant's name.

(2) Product name. Include the approved drug product's established name and proprietary name, if any.

(3) NDA, ANDA, and supplement number.

(4) Date of U.S. approval of NDA or ANDA.

(5) Date of postmarketing study commitment.

(6) Description of postmarketing study commitment. The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(7) Schedule for completion and reporting of the postmarketing study commitment. The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(8) Current status of the postmarketing study commitment. The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the

application or other agreed upon date:

(i) Pending. The study has not been initiated, but does not meet the criterion for delayed.

(ii) Ongoing. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iii) Delayed. The study is behind the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iv) Terminated. The study was ended before completion but a final study report has not been submitted to FDA.

(v) Submitted. The study has been completed or terminated and a final study report has been submitted to FDA.

(9) Explanation of the study's status. Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(2)(vii)(a)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(a)(7) of this section has changed since the last report.

(b) Public disclosure of information. Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for

failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in 20.61 of this chapter, or information, described in 20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii) Status of other postmarketing studies. A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix) Log of outstanding regulatory business. To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).

(3) Other reporting --(i) Advertisements and promotional labeling. The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 is available

on the Internet at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.

(ii) Special reports. Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(iii) Notification of a permanent discontinuance or an interruption in manufacturing. (a) An applicant of a prescription drug product must notify FDA in writing of a permanent discontinuance of manufacture of the drug product or an interruption in manufacturing of the drug product that is likely to lead to a meaningful disruption in supply of that drug in the United States if:

(1) The drug product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and

(2) The drug product is not a radiopharmaceutical drug product.

(b) Notifications required by paragraph (b)(3)(iii)(a) of this section must be submitted to FDA electronically in a format that FDA can process, review, and archive:

(1) At least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing; or

(2) If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated 6 months in advance, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

(c) Notifications required by paragraph (b)(3)(iii)(a) of this section must include the following information:

(1) The name of the drug subject to the notification, including the NDC for such drug;

(2) The name of the applicant;

(3) Whether the notification relates to a permanent discontinuance of the drug or an interruption in manufacturing of the drug;

(4) A description of the reason for the permanent discontinuance or interruption in manufacturing; and

(5) The estimated duration of the interruption in manufacturing.

(d)(1) FDA will maintain a publicly available list of drugs that are determined by FDA to be in shortage. This drug shortages list will include the following information:

(i) The names and NDC(s) for such drugs;

(ii) The name of each applicant for such drugs;

(iii) The reason for the shortage, as determined by FDA from the following categories: Requirements related to complying with good manufacturing practices; regulatory delay; shortage of an active ingredient; shortage of an inactive ingredient component; discontinuation of the manufacture of the drug; delay in shipping of the drug; demand increase for the drug; or other reason; and

(iv) The estimated duration of the shortage.

(2) FDA may choose not to make information collected to implement this paragraph available on the drug shortages list or available under section 506C(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) if FDA determines that disclosure

of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of the drug to patients). FDA will also not provide information on the public drug shortages list or under section 506C(c) of the Federal Food, Drug, and Cosmetic Act that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under 20.61 of this chapter.

(e) If an applicant fails to submit a notification as required under paragraph (b)(3)(iii)(a) of this section and in accordance with paragraph (b)(3)(iii)(b) of this section, FDA will issue a letter to the applicant informing it of such failure.

(1) Not later than 30 calendar days after the issuance of such a letter, the applicant must submit to FDA a written response setting forth the basis for noncompliance and providing the required notification under paragraph (b)(3)(iii)(a) of this section and including the information required under paragraph (b)(3)(iii)(c) of this section; and

(2) Not later than 45 calendar days after the issuance of a letter under paragraph (b)(3)(iii)(e) of this section, FDA will make the letter and the applicant's response to the letter public, unless, after review of the applicant's response, FDA determines that the applicant had a reasonable basis for not notifying FDA as required under paragraph (b)(3)(iii)(a) of this section.

(f) The following definitions of terms apply to paragraph (b)(3)(iii) of this section:

Drug shortage or shortage means a period of time when the demand or projected demand for the drug

within the United States exceeds the supply of the drug.

Intended for use in the prevention or treatment of a debilitating disease or condition means a drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

Life supporting or life sustaining means a drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Meaningful disruption means a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

(iv) Withdrawal of approved drug product from sale. (a) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are manufacturers, repackers, or relabelers subject to part 207 of this chapter must submit the following information about the drug, in accordance with the applicable requirements described in 207.61 and 207.65:

(1) The National Drug Code (NDC);

(2) The identity of the drug by established name and by proprietary name, if any;

(3) The new drug application number or abbreviated application number;

(4) The date on which the drug is expected to be no longer in commercial distribution. FDA requests that the reason for withdrawal of the drug from sale be included with the information.

(b) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are not subject to part 207 of this chapter must submit the information listed in paragraphs (b)(3)(iv)(a)(1) through (4) of this section. The information must be submitted either electronically or in writing to the Drug Registration and Listing Office, Food and Drug Administration, Center for Drug Evaluation and Research.

(c) Reporting under paragraph (b)(3)(iv) (a) of this section constitutes compliance with the requirements of 207.57 of this chapter to update drug listing information with respect to the withdrawal from sale.

(c) General requirements --(1) Multiple applications. For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2) Patient identification. Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe

that the reports do not represent actual results obtained.

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

21 C.F.R. § 314.94: Content and format of an ANDA

. . .

(a) ANDAs. Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the abbreviated new drug application that includes the following:

. . .

(8) Labeling --(i) Listed drug labeling. A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the ANDA, if the ANDA relies on a reference listed drug.

(ii) Copies of proposed labeling. Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) Statement on proposed labeling. A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences

approved under a petition filed under 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

21 C.F.R. § 314.97: Supplements and other changes to an approved ANDA

(a) General requirements. The applicant must comply with the requirements of 314.70 and 314.71 regarding the submission of supplemental ANDAs and other changes to an approved ANDA.

(b) Different listed drug. An applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current reference listed drug identified in the ANDA. This paragraph (b) applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (b), an applicant may supplement the ANDA to seek approval of a different strength.

21 C.F.R. § 314.98: Postmarketing reports

(a) Each applicant having an approved abbreviated new drug application under 314.94 that is effective must comply with the requirements of 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant must make the reports required under 314.81 and section 505(k) of the Federal Food, Drug, and Cosmetic Act for each of its approved abbreviated applications.

21 C.F.R. § 314.127: Refusal to approve an ANDA

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under 314.99:

. . .

(7) Information submitted in the ANDA is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the ANDA except for changes required because of differences approved in a petition under 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

CERTIFICATE OF COMPLIANCE

Pursuant to Massachusetts Rule of Appellate Procedure 16(k), I, Kannon K. Shanmugam, counsel for amicus curiae, certify that the foregoing brief complies with the rules of court that pertain to the filing of briefs, including Rule 16(e) (references to the record), Rule 16(f) (reproduction of relevant statutes and regulations), Rule 16(h) (length of briefs), Rule 18 (appendix to briefs), and Rule 20 (form of briefs),

s/ Kannon K. Shanmugam
KANNON K. SHANMUGAM
Pro Hac Vice Pending

OCTOBER 20, 2017

DECLARATION OF SERVICE BY MAIL

I, Kannon K. Shanmugam, counsel for amicus curiae, declare that I am over the age of eighteen years and not a party to or interested party in this action.

I further declare that, on October 20, 2017, I caused copies of the attached Brief of Amicus Curiae to be filed with the Clerk of the Court by placing one original and seventeen true copies thereof in a sealed envelope with postage fully paid, for shipment via Federal Express.

I further declare that I caused copies of the attached Brief of Amicus Curiae to be served by placing two true copies thereof in a sealed envelope with postage fully paid, for shipment via first-class U.S. mail to the following:

Counsel for Plaintiff-Appellant
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I further certify that all parties required to be served have been served.

I declare under penalty of perjury that the foregoing is true and correct.

Executed at Washington, D.C., October 20, 2017.

s/ Kannon K. Shanmugam
KANNON K. SHANMUGAM
PRO HAC VICE PENDING

OCTOBER 20, 2017