No. 12-142

IN THE
Supreme Court of the United States

MUTUAL PHARMACEUTICAL COMPANY, INC.,
Petitioner,

v.

KAREN L. BARTLETT,
Respondent.

On Writ of Certiorari to the United States Court of Appeals for the First Circuit

BRIEF OF PETITIONER MUTUAL PHARMACEUTICAL COMPANY, INC.

MICHAEL W. MCCONNELL
MICHAEL D. SHUMSKY
JOHN K. CRISHAM
KIRKLAND & ELLIS LLP
655 Fifteenth St. NW
Washington, DC 20005
(202) 879-5000
(202) 879-5200 (fax)
mcconne@kirkland.com
mshumsky@kirkland.com
jcrisham@kirkland.com

JAY P. LEFKOWITZ, P.C.
Counsel of Record
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
(212) 446-4800
(212) 446-4900 (fax)
lefkowitz@kirkland.com

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QUESTION PRESENTED

Whether the First Circuit erred in holding that federal law does not preempt state law design-defect claims targeting generic drug products because the conceded conflict between such claims and the federal laws governing generic drug design allegedly can be avoided if the makers of generic drugs simply stop selling their products.

CORPORATE DISCLOSURE STATEMENT

Pursuant to this Court's Rules 24.1(b) and 29.6, Petitioner Mutual Pharmaceutical Company, Inc. ("Mutual") incorporates the corporate disclosure statement contained in its previously filed Petition for Writ of Certiorari.

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INTRODUCTION

This case is controlled by a straightforward application of *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011). Two terms ago, that decision foreclosed state-law claims targeting generic drugs because the Hatch-Waxman Act imposes "an ongoing federal duty of sameness" that precludes generic drugs from deviating in any material respect from their brand-name equivalents. *Id*. at 2574-75 (internal quotation omitted). With the exception of the First Circuit's outlier decision in this case, literally dozens of courts thus have rejected lawsuits targeting generic drugs based on *Mensing*'s sameness rationale: Regardless of whether a state tort claim is captioned "failure to warn," "design defect," or something else entirely, these courts have recognized that the Constitution requires state law to yield if it would obligate a generic drug manufacturer to violate the federal sameness mandate as a precondition to engaging in interstate commerce.

The First Circuit was undeterred. It initially asserted that *Mensing* was limited to failure-to-warn claims, and thus did not implicate design-defect claims. PA10a-11a.[1] But the appellate court soon conceded that Hatch-Waxman's federal sameness mandate—and thus *Mensing*'s sameness rationale—

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[1] Citations to the PA reference the appendix accompanying Mutual's petition. Citations to the SPA reference the supplemental appendix accompanying Mutual's reply to respondent's brief in opposition. Citations to the JA reference the joint appendix. Citations to the CAA reference Mutual's First Circuit appendix.

applies equally to generic drug design and generic drug labeling. PA10a ("[T]he generic maker also cannot alter the composition of the drug."). And it recognized that failure-to-warn and design-defect claims equally thwart Congress's manifest intent to promote the sale of generic drugs. *Id*. ("[*Mensing*] held that Congress cannot have wanted the generic to pay damages under state law for a label that the FDA required. Mutual argues with some force that the generic maker also cannot alter the composition of the drug and so [Congress]'s policy of encouraging generics by preempting state tort claims should extend to design defect as well as [warning] claims.").

Even so, the appellate court held that respondent's state law design-defect claim did not conflict with Hatch-Waxman's sameness mandate, and thus survived *Mensing*'s preemption holding, because Mutual "certainly can choose not to make the drug at all." *Id*; PA10a-11a ("[T]he decision to make the drug and market it in New Hampshire is wholly [Mutual's] own.").

That is no answer. The *Mensing* defendants likewise were free not to make or market their drugs, and *Mensing* found preemption even though the Eighth Circuit had advanced this same "stop-selling" theory in the decision this Court reversed. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 611 (8th Cir. 2009) [*Mensing I*] ("The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient … they could have simply stopped selling the product."). Were the First Circuit's decision correct, *Mensing* thus would have come out the other way—as the court again conceded. PA11a ("[A] generic maker can avoid

defective warning lawsuits as well as design defect lawsuits by not making the drug.").

Nor is it any wonder why *Mensing* failed to embrace the Eighth Circuit's stop-selling rationale. This Court long ago recognized that state tort claims embody substantive state-law duties, and that tort verdicts like the one here thus establish that the defendant violated a state-law requirement. *See, e.g.*, *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324 (2008); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521-22 (1992) (plurality). Where the substantive state-law requirement embodied by a given tort claim conflicts with a contrary federal requirement, the ordinary operation of the Supremacy Clause prevents the state from enforcing its conflicting demand; were it otherwise, federal law no longer would be "the supreme Law of the Land." U.S. CONST. art. VI, cl. 2.

Contrary to the First Circuit's apparent belief, the stop-selling end-run does not avoid such conflicts. It only underscores that it is impossible for the manufacturer of a federally regulated product to fulfill its substantive federal and state obligations simultaneously, and ensures that state law prevails every time by letting juries impose liability *precisely because* the defendant complied with controlling federal standards from which it could not deviate without violating federal law. If the Supremacy Clause does anything, it forecloses this radical approach: Because every manufacturer can "choose" to stop making any product, no federal requirement ever could generate a direct preemptive conflict in a stop-selling world. *Mensing* rejected similar efforts to write ordinary conflict preemption out of the

Constitution, and there is no reason for departing from that decision here. 131 S. Ct. at 2579 ("We do not read the Supremacy Clause to permit an approach to pre-emption that renders conflict pre-emption all but meaningless.").

Ultimately, it is hard to imagine a result more at odds with Hatch-Waxman than this one. Even if the stop-selling theory could escape direct conflict preemption under *Mensing*, it wholly undermines the federal regime. Congress designed Hatch-Waxman to ensure that generic copies of previously approved drugs are available for sale whenever their costly branded equivalents come off patent; as *Mensing* said, "it is the special, and different, regulation of generic drugs that allowed the generic drug market to expand, bringing more drugs more quickly and cheaply to the public." 131 S. Ct. at 2582.

State-law verdicts that effectively order generic drugs withdrawn from interstate commerce *because* they complied with the federal sameness mandate eviscerate that core statutory objective. Indeed, such verdicts are particularly troubling today, when spiraling healthcare costs and concerns about growing federal deficits make Hatch-Waxman's goal of promoting price competition more important than ever before. And, finally, the stop-selling theory undercuts Congress's specific delegation to FDA of continually expanding authority to order approved drugs withdrawn from interstate commerce in the exercise of its expert judgment and subject to specific statutory protections for parties aggrieved by such orders. In sum, the stop-selling theory undercuts both Hatch-Waxman and the broader FDCA regime.

The decision should be reversed.

OPINIONS BELOW

The First Circuit's opinion is reported at 678 F.3d 30 and reprinted at PA1a-24a. The appellate court's errata is reprinted at PA27a-28a. The district court's opinion denying petitioner's renewed motion for judgment as a matter of law is reported at 760 F. Supp. 2d 220 and reprinted at PA29a-103a. The district court's opinion partially granting and partially denying petitioner's motion for summary judgment is reported at 731 F. Supp. 2d 135 and reprinted at PA106a-141a. The district court's unpublished order and opinion denying petitioner's motion for judgment on the pleadings is available at 2010 WL 3659789 and reprinted at PA142a-202a.

JURISDICTION

The First Circuit issued its decision and judgment on May 2, 2012, PA25a-26a, and the petition was timely filed on July 31, 2012. This Court has jurisdiction under 28 U.S.C. § 1254(1).

PERTINENT CONSTITUTIONAL AND STATUTORY PROVISIONS

The Constitution's Supremacy Clause provides:

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

U.S. CONST. art. VI, cl. 2.

The pertinent portions of the Federal Food, Drug, and Cosmetic Act are reproduced in Addendum A to this brief.

STATEMENT OF THE CASE

A. Statutory Background

1. The Statutory Scheme Before 1984

For nearly 75 years, the Federal Food, Drug, and Cosmetic Act ("FDCA") has governed the terms under which pharmaceutical products can be both marketed in and ordered withdrawn from interstate commerce. When Congress enacted the original FDCA in 1938, it for the first time required manufacturers to obtain FDA approval before selling a new drug. Pub. L. No. 75-717, ch. 675, § 505(a), 52 Stat. 1040, 1052 (1938) [the "1938 Act"] ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to [this Act] is effective with respect to such drug.").

To that end, the 1938 Act required applicants to submit to FDA an application that included (1) reports of clinical studies showing that "such drug is safe for use;" (2) a listing of all "components of such drug;" (3) a "statement of the composition of such drug;" (4) a description of "the methods ... facilities and controls used for … manufactur[ing], processing, and packing" the drug; (5) samples of the product and its components to the extent "the Secretary may require," and (6) proposed labeling for the drug. 1938 Act § 505(b), 52 Stat. at 1052. The Act in turn granted FDA broad authority to deny interstate marketing approval whenever it found a proposed drug would be unsafe, *id.* §505(d), 52 Stat. at 1052,

but presumed approvability by providing that applications would be deemed approved if the Agency did not reject them within 60 (or, in some cases, 180) days. *Id*. § 505(c), 52 Stat. at 1052.

The 1938 Act also directed FDA to determine when previously approved drugs should be removed from interstate commerce. It directed FDA to:

> suspend … [t]he effectiveness of an application with respect to any drug … if the [Agency] finds that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use.

Id. § 505(e), 52 Stat. at 1053 (enumeration omitted).

Not surprisingly, the law granted manufacturers significant protections in cases where FDA sought to exercise its new suspension authority. *First*, it provided that FDA could suspend interstate marketing approval only after providing the manufacturer with "due notice and opportunity for hearing." *Id*. *Second*, it required FDA to issue a written suspension "order [that] shall state the findings upon which it is based." *Id*. *Finally*, it provided aggrieved parties with a right to judicial review of any suspension decision in federal district court based on "the record [giving rise to] the order." *Id*. § 505(h), 52 Stat. at 1053.

Congress substantially expanded FDA's authority in 1962 by requiring it to consider drug efficacy in making approval and withdrawal decisions. Drug Amendments of 1962 [the "1962 Act"], Pub. L. No. 87-781, § 102(c), 76 Stat. 780, 781 (compelling FDA

to reject applications which "lack … substantial evidence that the drug will have the effect it purports or is represented to have"); *id.* § 102(d), 76 Stat. at 781-82 (requiring FDA to "withdraw approval … if [it] finds … a lack of substantial evidence that the drug will have the effect it purports or is represented to have").

The 1962 Act also repealed the *de facto* presumption that drugs were approvable; it now required *actual* FDA approval of a New Drug Application ("NDA") before interstate sales could commence. *Id.* § 104(a), 76 Stat. at 784 (barring the sale of any drug in interstate commerce "unless *an approval of* an application … is effective with respect to such drug") (emphasis added). And it bolstered FDA's authority to order approved drug products off the market by empowering the Agency to revoke interstate marketing approval in an array of new circumstances. *Id.* § 102(d), 76 Stat. at 781-82 (permitting, but not requiring, FDA to withdraw marketing approval based on recordkeeping failures; manufacturing, processing, and packing deficiencies; and labeling deficiencies).

Finally, the 1962 Act made two changes to the protections previously granted parties aggrieved by FDA's withdrawal authority. *First*, where FDA sought to exercise its permissive withdrawal authority, the statute required FDA to provide both "written notice … specifying the matter complained of" and an opportunity to correct the specified deficiencies "within a reasonable time" even before the Agency could proceed to notice and hearing on an actual withdrawal decision. *Id.* *Second*, Congress transferred judicial review of withdrawal orders from

the federal district courts to the federal appellate courts. *Id*. § 104(d)(1), 76 Stat. at 784.

2. The Hatch-Waxman Act

The early versions of the FDCA generally applied with equal force to all drugs—branded and generic alike. Virtually every manufacturer thus was required to submit an NDA that included its own safety and efficacy studies to secure and maintain interstate marketing approval. FDA, *Abbreviated New Drug Application Regulations—Final Rule* ["*Final ANDA Rule*"], 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992). That meant that even after the patents protecting a branded drug expired, virtually no generic copy could be approved until its manufacturer replicated the brand manufacturer's prior clinical studies.[2]

This had two consequences. *First*, the brand manufacturer benefited from a *de facto* extension of its patent monopoly. The patent laws at that time prevented generic companies from beginning clinical

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[2] There were two exceptions: FDA's so-called "DESI" regulation and its controversial "paper NDA" process. Under the DESI regulation, applicants could "submit information [to FDA] that showed the applicant's ability to manufacture a product … whose safety and effectiveness were equivalent to [a pre-1962] drug product whose safety and effectiveness had been established." *Final ANDA Rule*, 57 Fed. Reg. at 17950. The paper NDA process "permitted FDA to approve NDA's for post-1962 drug products [based on] safety and effectiveness information derived primarily from published reports based on well-controlled studies. This meant that manufacturers did not have to conduct their own tests, but adequate literature [to support approval] was [rarely] available." *Id*. at 17951.

studies until patent expiry, and those studies—once initiated—took years to complete. Laura J. Robinson, *Analysis of Recent Proposals to Reconfigure Hatch-Waxman*, 11 J. INTELL. PROP. L. 47, 52 (2003). Branded companies thus could maintain high prices long after patent expiry theoretically had opened the door to competition. *Second*, the extraordinary costs of conducting clinical studies were reflected in generic prices—meaning that the price of *all* drugs remained considerable even after competition began.

Not surprisingly, FDA approved few duplicate drugs under this regime; given the clinical trial requirements and the limited utility of the DESI and paper NDA processes, it simply was not cost-effective to develop and market generic drugs. In 1984, generics thus filled less than 19 percent of all prescriptions, Richard G. Frank, *The Ongoing Regulation of Generic Drugs*, 357 NEW ENG. J. MED. 1993 (2007), and hundreds of widely prescribed branded drugs lacked any generic equivalent. FTC, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, at 4 (July 2002), *available at* http://tinyurl.com/FTCStudy.[3]

By the early 1980s, Congress recognized that millions of Americans were unable to afford both the basic necessities of life and essential medications. It also recognized that state and federal authorities were wasting billions of dollars on costly branded drugs whose patent protection had expired. To remedy those problems and thereby "get generic

[3] All websites were visited and verified on January 13, 2013.

drugs into the hands of patients at reasonable prices—fast," Republican Senator Orrin Hatch and Democratic Representative Henry Waxman labored for years to establish an expedited approval pathway for generic drugs. *Andrx Pharms., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (quotation omitted); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1568 (Fed. Cir. 1997) ("[T]he purposes of the legislation are 'to make available more low cost generic drugs,'" and "'provide regulatory relief, increase competition, economy in government, and best of all, [allow] the American people [to] save money, and yet receive the best medicine that pharmaceutical science can provide.'") (quoting *inter alia* Statement On Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Doc. 1359, 1360 (Sept. 24, 1984)).

The resulting Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (Sept. 24, 1984)—more commonly known as the Hatch-Waxman Act—for the first time drew sharp distinctions between branded and generic drugs. While companies seeking to market an innovative drug product must continue to submit full NDAs (including clinical trial reports), *Mensing*, 131 S. Ct. at 2574 (citing 21 U.S.C. §§ 355(b)(1), (d)), applicants seeking to market copies of those drugs file only an Abbreviated New Drug Application ("ANDA") demonstrating the product's chemical and biological equivalence to a previously approved drug (called the "reference listed drug"). *Id.* (citing 21 U.S.C. § 355(j)(2)(A)).

To that end, the statute requires ANDA applicants to demonstrate that a proposed generic

drug is identical to its branded equivalent in all material respects—that is, that the generic product has the same design as its branded predecessor. ANDA applicants therefore must prove that the proposed generic drug contains "*the same*" active ingredient(s); employs "*the same*" route of administration (*e.g.*, oral or injected); presents "*the same*" dosage form (*e.g.*, tablet or capsule); exhibits "*the same*" strength (*e.g.*, 20mg or 40mg); and is "bioequivalent"[4] to its branded counterpart, in order to ensure it will "have *the same* therapeutic effect" as the branded equivalent. 21 U.S.C. § 355(j)(2)(A)(i)-(iv) (emphases added)[5]; *Mensing*, 131 S. Ct. at 2574 n.2 (explaining that each generic drug must be "*identical* [to its branded equivalent] in *active ingredients, safety, and efficacy*") (emphasis added).[6]

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[4] Generally speaking, two drugs are considered bioequivalent if there is "[no] significant difference in the rate and extent to which the active ingredient … becomes available at the site of action when administered at the same molar dose under similar conditions." 21 C.F.R. § 320.1(e).

[5] Unless otherwise noted, all citations to 21 U.S.C. § 355 are to the 2004 version of the statute, in place at the time of the events giving rise to this case.

[6] The statute does not require generic drugs to include the same *inactive* ingredients as the branded equivalent and thus empowers FDA to deny approval where "the inactive ingredients … are unsafe … or the composition of the drug is unsafe … because of the type or quantity of inactive ingredients included or the manner in which the[y] are included." 21 U.S.C. § 355(j)(4)(H) (enumeration omitted). The statute also allows applicants to petition FDA for permission to submit an ANDA "for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength

The net result of those requirements is that generic product design must be materially identical to that of its branded counterpart—which explains why, as *Mensing* recognized, generic product labeling must also be "'the same as the labeling approved for the [brand-name] drug.'" *Mensing*, 131 S. Ct. at 2574 (quoting 21 U.S.C. § 355(j)(2)(A)(v); citing *id.* § 355(j)(4)(G) (alteration in original)); *Final ANDA Rule*, 57 Fed. Reg. at 17961 ("[T]he ANDA product's labeling must be the same as the listed drug product's labeling *because* the listed drug product is the basis for ANDA approval.") (emphasis added).

There is no question that Hatch-Waxman has been wildly successful: By using the sameness mandate to streamline generic entry into interstate commerce and thereby expand access to affordable generic drugs, Hatch-Waxman has saved consumers literally trillions of dollars since enactment. *Mensing*, 131 S. Ct. at 2582 ("[I]t is the special, and different, regulation of generic drugs that allowed the generic drug market to expand, bringing more drugs more quickly and cheaply to the public."); HHS, *ASPE Issue Brief: Expanding the Use of Generic Drugs*, at 6 (Dec. 1, 2010), *at* http://tinyurl.com/HHSStudy ("[S]avings from the use of generic drugs for the total healthcare system were estimated to be $139.6 billion in 2009 [alone].").

B. The *Mensing* And *Demahy* Cases

Despite Hatch-Waxman's longstanding sameness requirement for generic drugs, its effect on state tort

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differ from that of a listed drug." *Id.* § 355(j)(2)(c). Neither exception to the sameness requirement is relevant here.

claims targeting generic drugs was unsettled until 2011, when this Court consolidated two cases for decision and held that Hatch-Waxman's sameness requirement preempts state-law tort claims targeting generic drugs.

In *Mensing* and *Demahy*, both plaintiffs alleged injuries resulting from metoclopramide, the generic version of branded Reglan®. Their complaints each included an array of state tort claims against the generic drug manufacturers, including strict liability for both failure to warn *and* design defect. First Am. Compl. ¶¶106-115, *Mensing v. Wyeth, Inc.*, No. 07-cv-3919 (D. Minn. filed Feb. 22, 2008); Compl. ¶¶37-42, *Demahy v. Wyeth*, No. 2:08-cv-03616-CJB-JCW (E.D. La. filed on removal June 2, 2008).

The generic manufacturers in *Mensing* moved to dismiss the plaintiff's complaint in its entirety as preempted by Hatch-Waxman's sameness mandate, and the district court—after explaining that all claims, including design defect, were "essentially 'failure to warn' claims"—granted the motion. *Mensing v. Wyeth, Inc.*, 562 F. Supp. 2d 1056, 1061 n.6 (D. Minn. 2008) ("[A]ll of Plaintiff's claims … are encompassed by the Court's preemption analysis.").

The Eighth Circuit reversed. It acknowledged that the federal sameness mandate prohibits manufacturers from altering generic drug warnings, but held the defendants could have complied with state law without violating that rule by asking FDA to authorize new warnings. *Mensing I*, 588 F.3d at 608-10. And it declared that state tort claims would not conflict with federal law even if that option was not available:

> The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product…. If Mensing's injuries resulted … they may be held liable.

Id. at 611.

While *Mensing* unfolded in Minnesota, *Demahy* was proceeding in federal court in Louisiana. As in *Mensing*, the generic manufacturer moved on preemption grounds to dismiss Demahy's lawsuit in its entirety, but this time the court denied the motion. *Demahy v. Wyeth, Inc.*, 586 F. Supp. 2d 642 (E.D. La. 2008). The Fifth Circuit then affirmed on interlocutory review, echoing the Eighth Circuit's assertion that the defendant at least could have discussed labeling changes with FDA, and further asserting that the sameness requirement applies only before FDA approval (leaving generic companies free to alter their labeling post-approval through the so-called "Changes Being Effected" or "CBE" process). *Demahy v. Actavis, Inc.* [*Demahy I*], 593 F.3d 428, 436-46 (5th Cir. 2010).

This Court granted *certiorari* in both cases and reversed—holding without qualification that "federal law pre-empts *these lawsuits*." *Mensing*, 131 S. Ct. at 2581 (emphasis added). The Court first rejected *Demahy*'s assertion that generic companies can use the CBE procedure to deviate from the branded product labeling after approval, because Hatch-Waxman's sameness requirement applies at all times. *Id.* at 2575-76. It next rejected the plaintiffs' contention that the generic manufacturers could

have sent "Dear Doctor letters" to healthcare practitioners without a corresponding letter from the brand manufacturer, since that "would inaccurately imply a therapeutic difference between the brand and generic drugs." *Id.* at 2576.

Finally, this Court refused to allow claims that the generic manufacturers at least could have "taken steps" to change their labeling by alerting FDA to the need for stronger warnings. *Id.* at 2579-82. Even though federal law permitted the defendants to do so, the Court rejected these claims because FDA would have had to authorize the new warnings before the defendants could have implemented them. *Id.* at 2581. Ultimately, the Court held the plaintiffs' lawsuits were preempted in their entirety: "[B]ecause pharmacists, acting in full accord with state law, substituted generic metoclopramide [for brand-name Reglan®], federal law pre-empts these lawsuits." *Id.* (citations omitted).

The plaintiffs then petitioned for rehearing, reiterating the Eighth Circuit's earlier assertion that the defendants could have complied with both the federal sameness mandate and their state-law tort duties *without* requiring FDA's involvement:

> Petitioners could have satisfied their duty under state tort law by suspending sales of the product with a label that they knew or should have known was inadequate. *See Mensing v. Wyeth, Inc.*, 588 F.3d 603, 611 (8th Cir. 2009). That course of action was always available to them and could have been accomplished independently, without any action by the FDA.

Resps.' Pet. for Reh'g, *Mensing*, 2011 WL 2874547, at *2 (July 18, 2011) (parenthetical omitted); *see also id.* at *1 ("The Court overlooks … that the Petitioner[s] could have independently complied with both state and federal law simply by suspending sales of generic metoclopramide.") (quotation omitted). This Court denied rehearing. *Actavis Elizabeth, LLC v. Mensing*, 132 S. Ct. 56 (2011); *PLIVA, Inc. v. Mensing*, 132 S. Ct. 55 (2011).

C. Facts and Proceedings

1. Sulindac

Sulindac is a non-steroidal anti-inflammatory drug ("NSAID") indicated for acute or long-term use in relieving the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder (subacromial bursitis/supraspinatus tendinitis), and acute gouty arthritis. JA553. FDA first approved sulindac for sale in September 1978, and Merck & Co., Inc. ("Merck") began marketing it as brand-name Clinoril®.

In May 1987, Mutual filed ANDAs seeking FDA approval to market generic sulindac, and FDA approved Mutual's products for interstate commercial sale on April 17, 1991 after finding them "safe and effective for use." CAA2169. There is no dispute that Mutual's sulindac is, and always has been, chemically and bioequivalent to Clinoril®, and that Mutual's sulindac labeling was materially identical to Clinoril®'s labeling. On October 22, 2002, FDA approved Mutual's request to conform its labeling to mirror changes in the Clinoril® labeling. CAA2171. That labeling was operative at all times relevant here, and repeatedly warned that sulindac therapy was associated with a rare but potentially

life-threatening dermatologic reaction known as Stevens-Johnson Syndrome and toxic epidermal necrolysis ("SJS/TEN"):

> WARNINGS
>
> ***
>
> Hypersensitivity
>
> Rarely, fever and other evidence of hypersensitivity (*see ADVERSE REACTIONS*) *including … severe skin reactions* have occurred during therapy with sulindac. *Fatalities have occurred in these patients…. If unexplained fever or other evidence of hypersensitivity occurs, therapy with sulindac should be discontinued.*
>
> ***
>
> ADVERSE REACTIONS
>
> ***
>
> Dermatologic…
>
> *Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and exfoliative dermatitis have been reported.*
>
> ***
>
> Hypersensitivity Reactions…
>
> *A potentially fatal apparent hypersensitivity syndrome has been reported.* This syndrome may include constitutional symptoms…, *cutaneous findings (rash or other dermatologic reactions—see above)*, conjunctivitis, involvement of major organs …, and other less specific findings.

JA553-554 (emphases added). There is no dispute that SJS/TEN is exceptionally rare; respondent's own expert testified that it occurs only in "one to two [people] per million." JA424.

In April 2005, FDA recommended that all NSAID manufacturers implement certain labeling changes. *See* FDA, COX-2 Selective (Includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ["FDA Request"], *at* http://tinyurl.com/NSAIDRequest. Consistent with FDA's request, Merck amended its Clinoril® labeling to include an additional warning regarding adverse dermatologic reactions (including SJS/TEN), and Mutual followed suit. JA555-556.

FDA also requested that NSAID manufacturers add a so-called "black box warning" regarding certain cardiovascular and gastrointestinal risks. *See* FDA Request. Those changes are irrelevant here, except that FDA (1) expressly considered and rejected adding language about SJS/TEN to the requested black box, and (2) reiterated its determination that NSAIDs other than Bextra® should remain available for sale in interstate commerce despite their known association with SJS/TEN. JA579-581 & n.8 (observing that "[w]hile other COX-2 selective and non-selective NSAIDs also have a risk for these rare, serious skin reactions, the reported rate for these serious side effects appears to be greater for Bextra"; concluding that only Bextra® had a sufficiently adverse risk/benefit profile to warrant withdrawing the product from interstate commerce; and observing that "[t]he risk for serious skin reactions is already included in the labeling for most [other] prescription NSAIDs").

FDA maintains its approval of both Merck's Clinoril® and Mutual's generic sulindac to this day.

2. Respondent's Use Of Sulindac

In December 2004, respondent Karen Bartlett sought treatment for acute shoulder pain. Her orthopedist prescribed Clinoril®, and her pharmacist eventually dispensed Mutual's generic sulindac pursuant to New Hampshire law. PA3a; *see also* N.H. Rev. Stat. Ann. § 318:47-d (2003) (allowing generic substitution). In 2005, respondent developed an especially severe case of SJS/TEN. PA3a.

There is no question that the results were horrific. Respondent suffered burns and burn-like wounds covering nearly two-thirds of her body. PA23a. Subsequent treatment required respondent to spend months in a medically-induced coma and undergo repeated eye surgeries. PA22a-23a. She now suffers from an array of permanent disabilities; she "cannot eat normally due to esophageal burns, cannot have sexual relations due to vaginal injuries, and cannot engage in aerobic activities due to lung injuries. She is almost blind now and faces some likelihood of complete and permanent blindness. She cannot read or drive or work. And she is seriously disfigured in face and body." PA23a.

3. Pretrial Proceedings

On January 8, 2008, respondent sued Mutual in New Hampshire state court. PA1a-4a. As in *Mensing* and *Demahy*, respondent's complaint raised an array of state-law claims—including both failure-to-warn and design-defect claims, JA57-80—and Mutual moved for judgment on the pleadings after removing the case to federal court. As Mutual

explained, federal law preempted the lawsuit both because it was impossible for Mutual to comply with Hatch-Waxman's sameness requirement and the alleged state-law duties, and because respondent's state-law claims otherwise frustrated Hatch-Waxman's goal of ensuring the sale of low-cost generic drugs. Mem. In Supp. of Mot. for J. on the Pleadings, 2008 WL 7027516, at 5-22 (Dec. 3, 2008).

The district court rejected Mutual's preemption defense on September 30, 2009. It began by effectively conceding that federal law precluded Mutual from altering the design of its generic product. PA165a-166a. It nonetheless rejected Mutual's preemption defense as to respondent's design-defect claim, reasoning that "[w]hile one way to avoid violating state law … would be to redesign Sulindac…, another way to do so would be to refrain from distributing it at all." PA165a. Because Hatch-Waxman did not compel Mutual to sell its FDA-approved product, the court asserted that there was no conflict between federal law and respondent's design-defect claim. PA165a-166a.

The court next rejected Mutual's argument that respondent's failure-to-warn claims were preempted. Like the Fifth Circuit's erroneous decision in *Demahy I*, the district court asserted that federal law did not prevent Mutual from unilaterally altering its labeling following FDA approval because Hatch-Waxman's sameness requirement allegedly applies only before approval. PA168a-197a. Finally, the court rejected Mutual's argument that respondent's state-law claims impermissibly undermined Hatch-Waxman's purposes and objectives. PA198a-202a.

Discovery followed, and Mutual eventually filed two motions for summary judgment. Mem. In Supp. of Summ. J. Based on Fed. Preemption ["Preemption MSJ"], 2010 WL 1371985 (Mar. 30, 2010); Mem. In Supp. of Summ. J. ["Causation MSJ"], 2010 WL 1371986 (Mar. 30, 2010). The first motion reiterated Mutual's earlier preemption arguments regarding the sameness requirement for generic drug labeling and, consistent with comment k to *Restatement (Second) of Torts* § 402A (1965), further explained that there is no distinction between failure-to-warn and design-defect claims for preemption purposes because "drugs are unavoidably unsafe products, and as such, cannot be defective in design as long as they are accompanied by adequate warnings." Preemption MSJ, 2010 WL 1371985, at 31-32; *see also Restatement (Second) of Torts* § 402A (1965), cmt. k ("There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs…. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous."). The district court treated the motion as one for reconsideration, PA139a, and denied it largely for the reasons it previously expressed. PA140a.

Mutual's second summary judgment motion argued that respondent's claims failed for lack of causation because discovery had revealed that respondent's prescribing physician never even read Mutual's labeling. Causation MSJ, 2010 WL 1371986, at 8-16. That meant *all* of respondent's claims were barred, since each depended on the alleged inadequacy of Mutual's FDA-mandated

warnings and since her physician's failure to read those warnings meant respondent's injuries could not have been caused by any alleged deficiency in the warnings. *Id.* at 17-20.

On July 12, 2010, the district court dismissed respondent's failure-to-warn claims on the foregoing causation grounds. PA117a-121a. But it denied Mutual's motion with respect to design defect, conceding that such claims necessarily turn on the adequacy of a drug's warnings, but asserting that the adequacy of petitioner's FDA-mandated labeling—which, again, respondent's physician never even read, and which Mutual repeatedly had explained it could not change—remained an issue for trial. PA124a-128a.

Respondent's remaining state-law claims then were dismissed either by court order (on various non-preemption grounds) or voluntarily. PA4a-5a.

4. Trial Proceedings

Those developments left only respondent's straight liability design-defect claim intact, and trial began in August 2010. Any possibility that trial would proceed as something other than a standard failure-to-warn case quickly evaporated. Although Mutual had withdrawn its comment k defense "for purposes of the trial of this matter," Notice of Withdrawal of Defenses, Dkt. No. 332, at 1 (Aug. 8, 2010), respondent's counsel began assailing the adequacy of Mutual's FDA-mandated labeling within minutes of introducing himself to the jury:

> [T]he evidence will show you that Sulindac was unreasonably dangerous *and had an inadequate warning, as well.* One of the

> easiest ways to show you this will be to show you that they got a new and better warning about six months after Karen Bartlett took the drug. You will learn that the label—the prescription drug label that went along with Sulindac before Karen Bartlett took the drug—[had] a reference to SJS and TEN in … the adverse reactions section of the label.
>
> You will learn that about six months after Karen Bartlett took this drug Mutual was ordered to put SJS and TEN in the warning section of the label for the first time ever. The label got better. They won't like that word better, but that's exactly what the evidence will show you is what happened.
>
> ***
>
> *You will hear much more evidence about why this label was inadequate in relation to this case.*

CAA1299-1301 (Trial Tr., Aug. 17, 2010, at 110-112) (emphases added).

Once witnesses took the stand, respondent's counsel continued to attack the adequacy of Mutual's FDA-mandated labeling:

> Mr. Jensen: [H]ave you assessed whether [petitioner's] label … has an effective or adequate warning for SJS/TEN?
>
> Dr. Tackett: I do not think it does have an adequate warning or effective warning.

SPA6a-7a.

> Mr. Jensen: The fact that [FDA later requested a labeling change], what if any bearing does that have on your opinion about the effectiveness or lack thereof of the prior Sulindac label?
>
> Dr. Tackett: Well, it definitely indicates the label was inadequate.

SPA9a.

> Mr. Jensen: What, if any, opinion have you reached as to whether or not [petitioner's] label had an effective warning for SJS and TEN?
>
> Dr. Tackett: As I've said before, I do not think it was effective. The new label basically has a better warning.

SPA12a.

Consistent with respondent's trial strategy, the district court ultimately instructed the jury that it could impose liability *only* if it found that Mutual's FDA-mandated warnings were inadequate:

> If you determine that Sulindac was unreasonably dangerous *and that a warning was not present and effective to avoid that unreasonable danger*, then you must find [respondent] has proven this element of her claim, a defect in design. However, if you determine that Sulindac was unreasonably dangerous, *but that a warning was present and effective to avoid that unreasonable danger*, then you must find for [petitioner].

SPA3a (emphases added).

The jury eventually awarded respondent over $21 million in damages, PA5a, and the district court denied petitioner's post-trial motions (including its renewed preemption arguments). PA69a-76a.

5. Appellate Proceedings

Mutual timely appealed, and the First Circuit affirmed on May 2, 2012. PA1a-26a. The appellate court began its preemption analysis by asserting that this Court "has yet to decide … [w]hether and to what extent the FDCA preempts design defect claims against generic drug manufacturers." PA8a. To answer that question, it turned to *Wyeth v. Levine*, 555 U.S. 555 (2009)—which, in contrast to *Mensing*, did not involve generic drugs at all. PA8a-9a. Even so, the appellate court asserted that *Wyeth* established a blanket rule "that state law serves as a 'complementary form of drug regulation.'" PA9a (quoting *Wyeth*, 555 U.S. at 578).

In contrast to *Wyeth*'s "general no-preemption rule," PA11a, the First Circuit claimed *Mensing* merely "carved out an exception to *Wyeth*, finding that the FDCA preempts *failure-to-warn* claims against *generic* drug manufacturers [because] the generic maker cannot alter the labeling." PA9a-10a (emphases in original). The court made no effort to explain how design-defect claims are distinguishable from the failure-to-warn claims *Mensing* rejected. Instead, it acknowledged (like the district court) that comment k conditions liability on the inadequacy of drug warnings. PA7a. And it admitted that *Mensing*'s sameness rationale in any event applies equally to labeling- and design-based claims: Just as federal law precludes manufacturers from altering

generic labeling, "Mutual cannot legally make sulindac in another composition." PA10a.

The court nonetheless theorized that the conflict between state-law design requirements and the federal sameness mandate would evaporate if generic manufacturers like Mutual simply refrained from engaging in the federally regulated conduct: "[Mutual] can choose not to make the drug at all; and the FDCA might permit states to tell Mutual it ought not be doing so if risk-benefit analysis weighs against the drug." *Id.* Yet it once again conceded that the stop-selling rationale cannot be squared with *Mensing*, where the same arguments had been made by the Eighth Circuit but not adopted by this Court. PA10a-11a (suggesting this Court might adopt the stop-selling theory "despite what [it] made of similar arguments in the labeling context").

The First Circuit ultimately punted the issue to this Court: "[I]t is up to the Supreme Court to decide whether *[Mensing]*'s exception is to be enlarged to include design defect claims." PA11a.

SUMMARY OF ARGUMENT

Mensing's sameness rationale applies equally to design-defect and failure-to-warn claims, and federal law thus equally preempts both sets of claims. That is so because Hatch-Waxman requires that *both* generic drug labeling *and* generic drug design be materially identical to the design and labeling FDA previously approved for the generic drug's branded equivalent. It therefore is impossible for a generic drug manufacturer to comply both with a state-law requirement that a generic drug's design be safer than the branded equivalent and with the federal requirement that the generic drug's design be

identical to its branded equivalent. State law design-defect claims, just like state law failure-to-warn claims, therefore are preempted by direct operation of the Supremacy Clause.

The stop-selling theory does not reconcile these conflicting state and federal design standards. It only confirms that it is impossible to comply simultaneously with the conflicting standards, and impermissibly ensures that state law prevails—by conditioning the manufacturer's right to engage in interstate commerce on conduct that would violate federal law, and by punishing manufacturers precisely because they complied with federal law. Indeed, if the stop-selling theory is right, there can never be direct conflict preemption; any conflict preemption defense would be foreclosed by the facile assertion that the manufacturer should have withdrawn from the regulated conduct altogether. This Court repeatedly has refused to adopt that radical approach to the Supremacy Clause, and there is no basis for reaching a different result here.

Even if the stop-selling theory somehow evades direct conflict preemption, its application here thoroughly undermines Hatch-Waxman's purposes and objectives. This Court long has recognized that Congress intended Hatch-Waxman's sameness requirement to promote the interstate commercial sale of generic drugs that share a previously approved drug's design, and that textually manifest intent is reflected throughout the statute. The stop-selling theory, by contrast, declares that generic drugs should be removed from the market despite Congress's clear intent to promote their sale. And, more broadly, the stop-selling theory undercuts both

Congress's delegation of vast authority to FDA to control the approval and withdrawal of drugs from interstate commerce *and* the specific statutory protections Congress granted parties aggrieved by the exercise of such authority.

ARGUMENT

I. Respondent's State Law Design-Defect Claim Directly Conflicts With The FDCA's Sameness Requirement.

Since *Mensing*, nearly every other court has rejected the First Circuit's stop-selling rationale for upholding the jury's design-defect verdict—including three federal appellate courts and scores of state and federal trial courts. *See, e.g.*, *Demahy v. Schwarz Pharma, Inc.* [*Demahy III*], __ F.3d __, No. 11-31073, 2012 WL 6698692, at *6 (5th Cir. Oct. 25, 2012) (holding that federal law preempts design-defect claims despite plaintiff's post-*Mensing* stop-selling arguments); *Mensing v. Wyeth* [*Mensing II*], 658 F.3d 867 (8th Cir. 2011) (vacating portion of pre-remand opinion embracing stop-selling theory despite plaintiff's post-*Mensing* assertion that the theory survived); *Smith v. Wyeth, Inc.*, 657 F.3d 420 (6th Cir. 2011) (finding preemption despite plaintiffs' post-*Mensing* stop-selling arguments); *see also* Pet. at 19, 25-27 (collecting cases).

As this widespread consensus underscores, there is no principled basis for reaching a different result here than in *Mensing*. Respondent's state law design-defect claim conflicts just as directly with Hatch-Waxman's federal sameness mandate as the claims everyone agrees *Mensing* held preempted, because the federal sameness mandate applies equally to generic drug design and generic drug

labeling. Nor does the stop-selling rationale reconcile these conflicting state and federal design requirements; it only underscores that it was impossible for Mutual to comply simultaneously with Hatch-Waxman's federal design requirement (to be the same as branded Clinoril®) and the state design requirement embodied in respondent's tort claim (to be different than branded Clinoril®).

A. *Mensing*'s Sameness Rationale Applies Equally To Design-Defect And Failure-To-Warn Claims.

The First Circuit recognized that *Mensing* rejected state tort claims challenging the adequacy of generic drug warnings on the ground that Hatch-Waxman's sameness requirement precludes generic manufacturers from altering their warnings. PA9a-10a ("In [*Mensing*], the Court [held] that [g]eneric manufacturers, unlike brand manufacturers, cannot unilaterally change their labels and thus cannot comply with both federal labeling standards and state law requirements deviating from those standards.") (citations omitted); *see also Mensing*, 131 S. Ct. at 2577 ("Federal [law] prevented the Manufacturers from independently changing their generic drugs' safety labels…. It [therefore] was not lawful under federal law for the Manufacturers to do what state law required of them."); *id.* at 2581 ("Here, state law imposed a duty on the Manufacturers to take a certain action, and federal law barred them from taking that action…. [Plaintiffs'] tort claims are pre-empted.").

The appellate court nonetheless thought it could evade *Mensing*'s holding by repeatedly asserting that the decision addressed only failure-to-warn claims—

not design-defect claims. PA9a ("[*Mensing* held only] that the FDCA preempts failure-to-warn claims.") (emphasis original); PA10a ("[T]he Supreme Court [has] not yet said it would extend [*Mensing*] to design defect claims."); PA11a ("[I]t is up to the Supreme Court to decide whether [*Mensing*] is to be enlarged to include design defect claims.").

That was error. Both the *Mensing* and *Demahy* complaints asserted failure-to-warn *and* design-defect claims (*supra* at 14), and those cases arrived here only after the lower courts found there was no basis for distinguishing among the myriad claims because each ultimately turned on the generic drug's FDA-mandated warnings. *Demahy III*, 2012 WL 6698692, at *6 ("Demahy's only remaining claims [were] characterized by the district court, this Court, and the Supreme Court as failure-to-warn claims."); *Mensing*, 562 F. Supp. 2d at 1061 n.6 ("[A]ll of Plaintiff's claims are essentially 'failure to warn' claims and are encompassed by the Court's preemption analysis."). That explains why *Mensing* held that "federal law pre-empts *these lawsuits*," not merely the claims plaintiffs had captioned "failure-to-warn." 131 S. Ct. at 2581 (emphasis added).

Even if it *Mensing* had been limited to failure-to-warn claims, the First Circuit provided no rationale for distinguishing between failure-to-warn and design-defect claims for preemption purposes—and there is none, as the First Circuit seemed to recognize. PA11a ("To refuse preemption here is … in tension … with … [*Mensing*]'s rationale."). That is so because Hatch-Waxman demands not only that generic *labeling* be "'the same as the labeling approved for the [brand-name] drug,'" *Mensing*, 131

S. Ct. at 2574 (quoting 21 U.S.C. § 355(j)(2)(A)(v) (alteration in original)), but also that generic *design* be the same. It thus requires each generic drug to contain "*the same*" active ingredient(s); employ "*the same*" route of administration; present "*the same*" dosage form; and exhibit "*the same*" strength as its branded equivalent, so that it will "have *the same* therapeutic effect" and safety profile as the branded equivalent. 21 U.S.C. § 355(j)(2)(A)(i)-(iv) (emphases added); *see also Mensing*, 131 S. Ct. at 2574 n.2 (explaining that generic drugs must be "identical in active ingredients, safety, and efficacy"). Indeed, Hatch-Waxman requires that generic labeling be materially identical to branded labeling *precisely because* generic design must be materially identical to branded design. *Final ANDA Rule*, 57 Fed. Reg. at 17961 ("[T]he ANDA product's labeling must be the same as the [branded] product's labeling *because* the [branded] drug product is the basis for ANDA approval.") (emphasis added).

Federal law thus gives manufacturers no more power to alter generic drug design than it does to alter generic drug labeling. Given the sameness mandate, generic manufacturers would violate federal law if they unilaterally altered *either* their FDA-mandated labeling *or* their FDA-mandated design; the resulting product could not lawfully be sold in interstate commerce. 21 U.S.C. § 355(a). Indeed, without the same active ingredient—sulindac, which is the design component to which respondent attributed her injuries—the resulting drug no longer would be a generic copy of a branded drug at all; it would be a different drug entirely.

Mensing's sameness rationale for rejecting claims challenging generic drug *labeling* thus applies with equal force to claims challenging generic drug *design*, because generic manufacturers "cannot comply with both a state law duty to make a safer design and the federal requirement that the generic drug design be the equivalent of the brand name drug." *Frazier v. Mylan Inc.*, __ F. Supp. 2d __, 2012 WL 6641626, at *6 (N.D. Ga. Dec. 18, 2012); *see also Aucoin v. Amneal Pharm.*, LLC, No. 11-1275, 2012 WL 2990697, at *9 (E.D. La. July 20, 2012) ("Defendant could not alter the design of the drug without violating federal law and this duty of sameness, making it impossible for Defendant independently to comply with both federal and state law."); *Johnson v. Teva Pharms. USA, Inc.*, 2012 WL 1866839, at *4 (W.D. La. May 21, 2012) ("The FDCA likewise prevented the Generic Defendants from altering unilaterally the design of the drug itself."); *Eckhardt v. Qualitest Pharm. Inc.*, 858 F. Supp. 2d 792, 801 (S.D. Tex. 2012) ("Generics were required to produce a drug that was equivalent to the brand-name drug and were not free to unilaterally pursue a safer alternative design."); *In re Darvocet*, No. 11-2226, 2012 WL 718618, at *3 (E.D. Ky. Mar. 5, 2012) ("[Plaintiffs] have not demonstrated that their so-called wrongful marketing claims escape preemption. The claims … are all based on the allegedly defective design of the drug, which the Generic Defendants, bound by their ongoing federal duty of sameness, were powerless to change.") (quotation omitted); *In re Pamidronate Prods. Liab. Litig.*, 842 F. Supp. 2d 479, 484 (E.D.N.Y. 2012) ("[T]he federal duty of sameness also applies in the context of generic drug design, and federal law preempts state laws imposing a duty

to change a drug's design.") (citation and quotation omitted); *Stevens v. PLIVA, Inc.*, No. 10-0886, 2011 WL 6224569, at *2 (W.D. La. Nov. 15, 2011) ("Under the same federal law analyzed in *Mensing*, a generic pharmaceutical product must be the same as [its branded equivalent] in active ingredients, safety and efficacy and hence, as was the case with labeling, federal law pre-empts state laws imposing the duty to change a drug's design.") (citation omitted).

Indeed, design-defect claims are preempted not only under *Mensing*'s sameness *rationale*; they are preempted even under the narrow *holding* that the First Circuit attributed to *Mensing*—*i.e.*, that "the FDCA preempts failure-to-warn claims against generic drug manufacturers." PA9a. After all, this Court recognized just last year that failure-to-warn claims are in fact design-defect claims. *Kurns v. Railroad Friction Prods. Corp.*, 132 S. Ct. 1261, 1268 (2012) ("A failure-to-warn claim alleges that a product is defective."); *id.* at 1268 n.4 ("A failure-to-warn claim imposes liability on a particular design … and the accompanying threat of liability will inevitably influence a manufacturer's choice whether to use that particular design."). That recognition forecloses the First Circuit's attempt to draw a bright line between failure-to-warn and design-defect claims for preemption purposes; it underscores that *Mensing* in fact encompassed design-defect claims, whether they were labeled as such or not.

Perhaps more important, the flipside of *Kurns*'s insight regarding the nature of failure-to-warn claims is equally true: At least in the prescription-drug context, *design-defect claims are failure-to-warn claims*. That is so because New Hampshire (like the

overwhelming majority of states, *see* Addendum B) follows comment k to *Restatement (Second) of Torts* § 402A—as the First Circuit recognized, PA7a, and respondent unequivocally has conceded here. BIO 3-4. Because such products are "unavoidably unsafe," comment k renders them "exempt from strict liability" so long as they are "'properly prepared, and accompanied by proper directions and warning.'" BIO 4 (quoting comment k). Accordingly, whatever distinctions there may be between design-defect and failure-to-warn claims outside this context, those claims collapse together in cases targeting drugs.[7]

As Mutual thus explained below, respondent's design-defect claim never should have gone to trial because it necessarily and impermissibly hinged on challenging the adequacy of Mutual's FDA-mandated warnings. Preemption MSJ, 2010 WL 1371985, at 31-32 ("[D]rugs are unavoidably unsafe products, and as such, cannot be defective in design as long as they are accompanied by adequate warnings. As such, any design claim directly implicates warnings and thus, falls under the same preemption analysis.").[8]

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[7] Indeed, even outside the comment k context, New Hampshire law requires consideration of the adequacy of a product's warnings as part of its standard design-defect analysis. *Price v. BIC Corp.*, 142 N.H. 386, 389 (N.H. 1997) ("[W]hether a product's design is unreasonably dangerous [requires] evaluation of many conflicting factors [including] the presence and efficacy of a warning to avoid an unreasonable risk of harm.") (quotation omitted).

[8] The appellate court seemed to fault Mutual for withdrawing its comment k defense for trial purposes and thereby refusing to defend the adequacy of its FDA-mandated warnings in court. PA7a-8a & n.1. That is entirely backwards: Mutual's whole

Indeed, the district court's eventual jury instructions sharply underscored this fatal defect in respondent's design-defect claim:

> If you determine that Sulindac was unreasonably dangerous *and that a warning was not present and effective to avoid that unreasonable danger*, then you must find [respondent] has proven this element of her claim, a defect in design. However, if you determine that Sulindac was unreasonably dangerous, *but that a warning was present and effective to avoid that unreasonable danger*, then you must find for [petitioner].

SPA3a (emphases added).

Accordingly, the First Circuit did not err merely because *Mensing*'s sameness rationale applies equally to both design-defect and failure-to-warn claims. It erred because the jury's verdict ultimately hinged as a matter of state law on the one thing everyone agrees *Mensing* held it could not: a decision that Mutual's FDA-mandated labeling was inadequate. *Mensing* thus squarely forecloses the sole claim on which the jury based its verdict.

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point is (and always was) that Hatch-Waxman's sameness requirement placed Mutual's FDA-mandated labeling beyond the jury's purview, since (as *Mensing* later held) the sameness requirement precluded Mutual from altering those warnings. It would defy *Mensing* to suggest that Mutual somehow was obligated to prove as a factual matter at trial what Hatch-Waxman establishes as a matter of federal law.

B. Respondent's Stop-Selling Theory Only Exacerbates The Conflict Between State And Federal Law.

The First Circuit acknowledged that Hatch-Waxman's sameness mandate grants generic manufacturers no more power to alter the design of their drugs than it does to alter the labeling of their drugs. PA10a ("Mutual cannot legally make sulindac in another composition (nor is it apparent how it could alter a one-molecule drug anyway)."). And it recognized that design-defect liability in New Hampshire turns on the adequacy of a product's warnings. PA7a ("[A]n ordinary consumer would hardly know without further warning that sulindac … carries a risk of the kind of ill effects and suffering that Bartlett encountered.").

The court nonetheless asserted that finding preemption here would conflict with *Wyeth*'s alleged adoption of "a general no-preemption rule," PA11a, and held that any conflict between Hatch-Waxman's sameness mandate and respondent's state-law claim could be avoided if Mutual simply pulled its products off the market. PA10a ("[Mutual] certainly can choose not to make the drug."); PA10a-11a ("[T]he decision to make [sulindac] and market it in New Hampshire is wholly [Mutual's]."). Neither assertion resolves the direct conflict between the federal and state generic drug design requirements at issue here.

The First Circuit's reliance on *Wyeth* is simply bizarre. Unlike *Mensing*, *Wyeth* concededly did not involve generic drugs *or* design-defect claims. PA9a & n.2 ("*Wyeth*'s holding was technically limited to failure-to-warn claims…. More specifically, *Wyeth* held that the FDCA does not preempt failure-to-warn

claims against brand-name drug manufacturers.") (citing *Wyeth*, 555 U.S. at 568, 573). Nor did *Wyeth* "adopt[] a general no-preemption rule." PA11a. It merely held that a state-law claim challenging Wyeth's warnings could proceed because federal law specifically authorized Wyeth to change those warnings unilaterally. *Wyeth*, 555 U.S. at 571 ("[W]hen the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval."). As *Mensing* recognized, *Wyeth* thus stands for the unremarkable proposition that state law can hold the manufacturer of a federally regulated product liable where federal law expressly empowers that manufacturer to alter its product to comply with the substantive duty embodied in the plaintiff's tort claim. *Mensing*, 131 S. Ct. at 2581 ("[T]he federal regulations applicable to Wyeth allowed the company, of its own volition, to strengthen its label in compliance with its state tort duty … to provide an adequate warning label.").

That proposition has no applicability here, because it is beyond dispute that federal law gave Mutual no such power. As the appellate court recognized, the federal sameness requirement barred Mutual from altering sulindac's design to comply with New Hampshire's demand that its drug be safer than brand-name Clinoril®, PA10a, just as the federal sameness requirement barred the *Mensing* defendants (but not the *Wyeth* defendant) from altering their drug labels to comply with state tort-law demands to more "safely label their products"

than those products' branded equivalents. *Mensing*, 131 S. Ct. at 2577.

Faced with that reality, the First Circuit ultimately asserted that it remained possible for Mutual both to design its product to comply with Hatch-Waxman's federal sameness requirement and then choose not to sell that product if it wanted to avoid state tort liability. PA10a-11a. It therefore held respondent's design-defect claim survived Mutual's preemption defense, "despite what the Supreme Court made of similar arguments" advanced in the Eighth Circuit's pre-*Mensing* opinion. PA10a; *see also Mensing I*, 588 F.3d at 611 ("The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient … they could have simply stopped selling the product.").

The First Circuit offered no reason why the result should be any different here than in *Mensing*, which of course reversed the Eighth Circuit's decision. It simply asserted that this Court might reach the opposite result out of sympathy for respondent. PA11a ("Bartlett having lost her warning claim by the mere chance of her drug store's selection of a generic, the Supreme Court might be less ready to deprive Bartlett of her remaining avenue of relief."[9]). But this Court left no doubt that Congress's "special, and different, regulation of generic drugs" required

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[9] The court's assertion that respondent "lost her warning claim" because of *Mensing* misses the mark. Respondent never had a "warning claim" against Mutual because her physician never read Mutual's warnings. PA117a.

preemption, even as it "acknowledge[d] the unfortunate hand that federal drug regulation has dealt Mensing, Demahy, *and others similarly situated*." 131 S. Ct. at 2581-82 (emphasis added). The same federal law addressed in *Mensing*—Hatch-Waxman's sameness mandate—applies no less to claims targeting generic drug design than claims targeting generic drug labeling, and the admittedly tragic facts of this case are not grounds for jettisoning *Mensing*'s straightforward application of the Supremacy Clause.

Indeed, this Court made clear even before *Mensing* that the appellate court's radical theory of liability does not resolve the direct conflict between state and federal law; rather, it perversely ensures that state law reigns supreme, by conditioning the right to engage in interstate commerce free from state-law liability on conduct that would violate federal law. The Supremacy Clause forbids that approach. This Court long ago held that state law "is pre-empted by direct operation of the Supremacy Clause" where it prevents "the exercise of … federally protected rights." *Brown v. Hotel & Rest. Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984). And it likewise has recognized that state tort law directly and thus impermissibly conflicts with federal law even though it remains possible for the manufacturer of a federally regulated product to both comply with federal law and pay damages to state tort plaintiffs who later demonstrate that the manufacturer's compliance with federal standards violated state law. *See, e.g.*, *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324 (2008); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521-22 (1992) (plurality) & *id.* at 548-49 (Scalia, J.,

concurring in relevant part); *see also MacDonald v. Monsanto Co.*, 27 F.3d 1021, 1025 (5th Cir. 1994); *Shaw v. Dow Brands, Inc.*, 994 F.2d 364, 370 (7th Cir. 1993); *Palmer v. Liggett Group, Inc.*, 825 F.2d 620, 627 (1st Cir. 1987).

That is so because "common-law liability is 'premised on the existence of a legal duty,' and a tort judgment therefore establishes that the defendant has violated a state-law obligation." *Riegel*, 552 U.S. at 324 (quoting *Cipollone*, 505 U.S. at 522); *Cipollone*, 505 U.S. at 521 ("As we noted in another context, 'state regulation can be as effectively exerted through an award of damages as through some form of preventive relief.'") (quoting *San Diego Bldg. Trades Council v. Garmon*, 359 U.S. 236, 247 (1959)); *cf. Plains Commerce Bank v. Long Family Land & Cattle Co.*, 554 U.S. 316, 331-32 (2008) ("[T]ribal tort law … regulates the substantive terms on which the Bank is able to offer its fee land for sale [and] is a form of regulation.") (citing *Riegel*, 552 U.S. at 324).

It thus is irrelevant that "the common-law remedy is limited to damages," which of course can be paid by unsuccessful tort defendants (just as defendants can avoid even the possibility of damages liability by pulling their products from interstate commerce). *Riegel*, 552 U.S. at 324. Whether or not a defendant is capable of writing a check because it "chose" to comply with controlling federal standards instead of contrary state requirements, the fact remains that those federal standards directly conflict with "the legal duty that is the predicate of the common-law damages action." *See, e.g.*, *Cipollone*, 505 U.S. at 524; *Riegel*, 524 U.S. at 324 ("[A] liability award can be, indeed is designed to be, a potent

method of governing conduct.") (quotations omitted); *see also Wyeth*, 555 U.S. at 590 (Thomas, J., concurring) ("[I]f federal law gives an individual the right to engage in certain behavior that state law prohibits, the laws would give contradictory commands notwithstanding the fact that an individual could comply with both by electing to refrain from the covered behavior.") (citing Caleb Nelson, *Preemption*, 86 VA. L. REV. 260-61 (2000)).

If the Supremacy Clause preempts state-law *damage awards* predicated on a standard that conflicts with federal law, it surely preempts states from enforcing the same conflicting standard by *banning the sale of a federally compliant product altogether*. The same principle applies in both cases, and is perfectly illustrated here. Even if Mutual's FDA-mandated warnings played no role in this case—and they assuredly did—the legal duty giving rise to respondent's design-defect claim under New Hampshire law directly conflicts with Hatch-Waxman's federal sameness mandate. Under New Hampshire law, Mutual's basic duty was to "design [its drug] reasonably safely for the uses [Mutual] can foresee." *Thibault v. Sears, Roebuck & Co.*, 118 N.H. 802, 809 (1978). The jury's verdict "therefore establishes that [Mutual] violated a state-law obligation" to design its drug to be "reasonably safe" under the jury's *ad hoc* interpretation of that standard. *Riegel*, 552 U.S. at 324.

The problem, of course, is that Hatch-Waxman establishes a different design standard: It required Mutual's sulindac design to be "the same" as brand-name Clinoril®, 21 U.S.C. § 355(j)(2)(A), in order to guarantee that Mutual's generic drug would be

"identical" to brand-name Clinoril® in terms of both "safety, and efficacy." *Mensing*, 131 S. Ct. at 2574 n.2. Federal law thus forbade Mutual from satisfying its state-law obligation to design a product with a different safety profile than the one FDA approved (and continues to approve). PA10a ("Mutual cannot legally make sulindac in another composition."). If the Supremacy Clause means anything, it means that state law cannot condition the right to engage in interstate commerce on conduct that would violate federal law or punish parties for complying with controlling federal standards from which they cannot lawfully deviate; the substantive duty embodied in respondent's design-defect claim unquestionably is a "Thing in the Constitution or Laws of any State to the Contrary," and therefore must yield to federal law. U.S. CONST. art VI, cl. 2.

The First Circuit's facile assertion that Mutual could have "cho[sen] not to make the drug at all," PA10a, thus does nothing to *reconcile* the direct conflict between the state and federal design standards. It only highlights that it was *impossible* for Mutual to comply simultaneously with Hatch-Waxman's federal design requirements and the jury's *ad hoc* interpretation of New Hampshire's apparently contrary design requirements. That is what impossibility *means*: that a person cannot comply simultaneously with both state and federal standards, and thus must cease acting at all.

Accepting the First Circuit's stop-selling rationale thus would foreclose ordinary conflict preemption of state tort claims involving *any* federally regulated product. Because *every* manufacturer can in theory

"choose" to stop making a given product, no federal requirement could ever generate a direct preemptive conflict. *See In re Darvocet*, 2012 WL 718618, at *3 ("[T]he idea that [the generic defendants] should have simply stopped selling propoxyphene is an oversimplified solution that could apply anytime the issue of impossibility preemption arises: avoid a conflict between state and federal law by withdrawing from the regulated conduct altogether.").

Indeed, the appellate court's radical theory of liability would produce an array of absurd results. If, for instance, the State of California required pharmacists to dispense medical marijuana as a condition of doing business in the state—and thereby violate the federal Controlled Substances Act—no serious person would suggest the California law survives the pharmacist's preemption defense simply because federal law does not compel anyone to be a pharmacist. Yet that is precisely what the First Circuit held in this case: Because the pharmacist in theory can "comply" with both state and federal law by "choosing" not to be a pharmacist at all, she would have no defense.

Or suppose state law allows the governor to fire employees who do not contribute to her reelection campaign. The First Amendment conflicts with that law, and under the Supremacy Clause thus trumps the state law. It used to be said there was no conflict because the employee could cease working for the state (and indeed had no right to do so in the first place). *See McAuliffe v. Mayor of New Bedford*, 155 Mass. 216, 220 (1892) (Holmes, J.) ("[P]etitioner may have a constitutional right to talk politics, but he has

no constitutional right to be a policeman."). That view, of course, has been repudiated for decades. *See, e.g.*, *O'Hare Truck Serv., Inc. v. City of Northlake*, 518 U.S. 712, 716-17 (1996). Yet the First Circuit's "stop-selling" theory is logically indistinguishable from the "stop-working" theory. The option of withdrawing from the field does not eliminate the conflict between the state requirement and federal authorization. It is just a way to ensure state law prevails over federal law.

That *cannot* be correct—and *Mensing* made clear it *is* not correct, by declaring that this Court could "not read the Supremacy Clause to permit an approach to pre-emption that renders conflict pre-emption all but meaningless. The Supremacy Clause, on its face, makes federal law 'the supreme Law of the Land' even absent an express statement by Congress." 131 S. Ct. at 2579 (quoting U.S. CONST. art. VI, cl. 2). That commonsense holding controls here, and the decision should be reversed.

II. Respondent's State Law Design-Defect Claim Eviscerates The FDCA's Purposes and Objectives.

Even if it did not directly conflict with Hatch-Waxman's sameness requirement—and it does—respondent's state law design-defect claim still would be preempted. For more than 70 years, this Court has made clear that the Supremacy Clause preempts any state law (including any tort claim) that "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" even absent a direct conflict with federal law. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941); *see also Williamson v. Mazda Motor of Am., Inc.*, 131 S. Ct.

1131, 1136 (2011); *Geier v. American Honda Motor Co.*, 529 U.S. 861, 881-82 (2000); *International Paper Co. v. Ouellette*, 479 U.S. 481, 493 (1987); *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 156 (1982); *Perez v. Campbell*, 402 U.S. 637, 649-50 (1971). Respondent expressly concedes the legitimacy of this well-settled rule. BIO 27-28 ("Federal law continues to preempt state tort suits that frustrate the accomplishment of Congress's purposes and objectives, regardless of whether the defendant could comply with state law by suspending sales of its product.").[10]

If ever there were a case for purposes-and-objectives preemption, this is it. The stop-selling end-run around Hatch-Waxman's federal sameness requirement self-consciously undermines Congress's manifest intent to ensure the sale of generic copies of FDA-approved drug designs, by ordering those products off the market precisely because they replicate FDA-approved designs.

A. The Stop-Selling Theory Thwarts Hatch-Waxman's Central Objective Of Ensuring That Generic Drugs Are Available For Sale In Interstate Commerce.

This Court repeatedly has explained that Hatch-Waxman's central objective is to ensure that generic copies of previously approved drugs are available for sale in interstate commerce whenever their costly brand-name equivalents come off patent. *See, e.g.*,

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[10] Given the parties' unqualified agreement that *Hines* supplies the proper constitutional test, there is no reason to question its legitimacy here.

Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1676 (2012) ("Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. *As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market*.") (citation omitted; emphasis added; referencing *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990) ("[T]o enable new drugs to be marketed more cheaply and quickly, [Hatch-Waxman] substantially shorten[ed] the time and effort needed to obtain [generic] marketing approval.") (citation omitted)); *Mensing*, 131 S. Ct. at 2582 ("[I]t is the special, and different, regulation of generic drugs that allowed the generic drug market to expand, bringing more drugs more quickly and cheaply to the public.").

And unlike other cases—where assessing Congress's intent arguably depends "on extratextual judicial suppositions," or requires courts to "wade[] into a sea of agency musings and Government litigating positions," *Williamson*, 131 S. Ct. at 1142 (Thomas, J., concurring)—this Court's longstanding assessment of Hatch-Waxman's core objectives stems directly from "federal standards and policies that are set forth in, or necessarily follow from, the statutory text that was produced through the constitutionally required bicameral and presentment procedures." *Wyeth*, 555 U.S. at 586 (Thomas, J., concurring). Indeed, nearly every subsection of Hatch-Waxman's generic-drug provisions reflects Congress's textually manifest goal of ensuring that such drugs are available to compete for sales in the interstate

marketplace, beginning with the title Congress selected: "the *Drug Price Competition* and Patent Term Restoration Act of 1984." Hatch-Waxman Act, 98 Stat. at 1585 (emphasis added); *see also INS v. National Ctr. for Immigrants' Rights, Inc.*, 502 U.S. 183, 189 (1991) ("[T]he title of a statute or section can aid in resolving an ambiguity."); *United States v. Fisher*, 6 U.S. (2 Cranch) 358, 386 (1805) (Marshall, C.J.) ("[T]he title claims a degree of notice, and will have its due share of consideration.").

To that end, Hatch-Waxman's substantive provisions seek to both facilitate and encourage the sale of generic drugs that share previously approved designs. The statute begins by creating an "abbreviated" pathway that expressly requires FDA to approve bioequivalent generic drugs that use "*the same*" active ingredient(s), routes of administration, dosage forms, and strengths as previously approved brand-name drugs. Hatch-Waxman Act, § 101, 98 Stat. at 1585-86 (emphasis added; codified at 21 U.S.C. § 355(j)(1)-(2)(A)); *id.*, 98 Stat. at 1587 ("[FDA] shall approve an [ANDA] unless [the sameness criteria are not met].") (codified at 21 U.S.C. § 355(j)(4)). Again, this Court long has recognized that these provisions evince Congress's intent to make generic copies of previously approved drug designs available for sale whenever branded patents expire. *See, e.g.*, *Caraco*, 132 S. Ct. at 1676; *Mensing*, 131 S. Ct. at 2582; *Eli Lilly*, 496 U.S. at 676.

To ensure prompt FDA action on generic *applications* and thereby expedite the entry of generic *products* into interstate commerce, Hatch-Waxman next provides that the Agency "may not require that an abbreviated application contain

information in addition to that required by [the sameness] clauses." Hatch-Waxman Act, § 101, 98 Stat. at 1586 (codified at 21 U.S.C. § 355(j)(2)(A)). And it directs FDA to either approve or disapprove each submitted ANDA "[w]ithin [180] days" unless the applicant agrees otherwise. *Id.*, 98 Stat. at 1588 (codified at 21 U.S.C. § 355(j)(4)(A)).

Finally, to ensure generic manufacturers take full advantage of the abbreviated pathway, Hatch-Waxman creates a lucrative incentive for generic applicants to both challenge competition-blocking patents and submit ANDAs at the earliest chance: It rewards the first generic applicant that submits an ANDA that challenges a patent which covers the referenced name-brand drug with a 180-day exclusivity period during which no other ANDA for that drug can be approved. *Id.*, 98 Stat. at 1589 (codified as amended at 21 U.S.C. § 355(j)(5)(B)(iv)).

As with Hatch-Waxman's sameness provisions, the courts repeatedly have recognized that Congress intended the 180-day exclusivity provision to drive marketplace competition by ensuring not only that generic products *can* enter interstate commerce, but that they *actually do so*—both early and often. *See, e.g.*, *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1305 (D.C. Cir. 2010) ("This promise of initial marketing exclusivity is thus intended to increase competition by expediting the availability of generic equivalents."); *Teva Pharms., USA, Inc. v. Leavitt*, 548 F.3d 103, 106 (D.C. Cir. 2008) ("The legislative purpose underlying [180-day exclusivity] is to enhance competition by encouraging generic drug manufacturers to challenge the patent information provided by NDA holders in order to bring generic

drugs to market earlier."); *see also Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1283 (Fed. Cir. 2008); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006).

Suffice it to say, the stop-selling theory cannot be squared with the legislative objectives manifested by these specific statutory provisions—each of which is calibrated not only to *allow* interstate commercial sale of generic drugs that share a previously approved design, but to *ensure* that such drugs enter interstate commerce as often and early as possible. Accepting the appellate court's stop-selling theory of liability thus "would take [away] the very ability to achieve the law's congressionally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect." *Geier*, 529 U.S. at 872.

The legislative history accompanying Hatch-Waxman confirms what the statutory text makes clear: Congress intended to ensure that generic copies of previously approved drug designs are available for sale in interstate commerce whenever their branded equivalents come off patent. As the House Report explained, "[t]he purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962…. The availability of generic versions of pioneer drugs approved after 1962 would save Americans $920 million over the next 12 years." H. Rep. 98-857 pt. 1, at 14-17 (1984).

Key players in the debate repeatedly echoed that view. Representative Waxman explained:

> [This bill] is the most important drug legislation to come before the Congress since the 1962 [Act]. It is also the most important consumer legislation to be considered this Congress. The bill will save consumers over $1 billion by making more low cost generic drugs available.
>
> ***
>
> Unfortunately, the[] abbreviated generic drug approval procedures [for certain pre-1962 drugs] do not apply to pioneer drugs approved after 1962. The lack of such procedures is an effective bar to generic competition because the generic companies cannot afford the millions of dollars to duplicate the test results already in the FDA's files.
>
> ***
>
> By making these drugs available as generics, H.R. 3605 will reduce the cost of drugs for all consumers.

130 Cong. Rec. H8706 (Aug. 8, 1984) (statement of Rep. Waxman).

The legislative history also underscores that Congress deliberately required generic drug design to be materially identical to branded drug design because FDA already approved that design—which is the only way Congress could both eliminate the clinical study requirement *and* ensure that patient safety would not be compromised by generic drugs. *See, e.g.*, 130 Cong. Rec. H8703 (Aug. 8, 1984) (statement of Rep. Derrick) ("[P]harmaceutical companies which produce generic drugs must

undertake a lengthy and expensive procedure in order to gain FDA approval for sale of a drug … *despite the fact that … FDA has previously approved the sale of the exact same drug by the company holding the patent. This bill seeks to end this duplication of effort and, more importantly, make it easier for pharmaceutical companies to market cheaper, generic alternatives*.") (emphasis added); 130 Cong. Rec. H9144 (Sept. 6, 1984) (statement of Rep. Walgren) ("[This legislation] will make hundreds of new low-cost, generic drugs available by speeding up the approval process for these drugs. As the current law stands, [post-1962 drugs] can only be made available in generic form through a long and involved testing process. *This process is unnecessary because the active ingredient in the generic drug is identical to that in the name-brand drug. Under H.R. 3605, this testing process would be speeded up tremendously without endangering the safety to the consumer*.") (emphasis added).

There is thus no question that the stop-selling theory thwarts Congress's goal of ensuring that generic copies of previously approved drug designs are available to compete for sales in interstate commerce. Whereas federal law authorizes and encourages the sale of such products in interstate commerce, the stop-selling theory by design seeks to punish companies like Mutual for doing just that. This Court repeatedly has rejected far less dramatic state efforts to undermine federal objectives. *See, e.g.*, *Kurns*, 132 S. Ct. at 1269 (rejecting as "contrary to common sense" arguments that federal law preempts state-law claims targeting railroad operators but not locomotive manufacturers because "a railroad's ability to equip its fleet of locomotives in

compliance with federal standards is meaningless if manufacturers are not allowed to produce locomotives … that meet those standards"); *Engine Mfrs. Ass'n v. South Coast Air Quality Mgmt. Dist.*, 541 U.S. 246, 255 (2004) (explaining it "would make no sense" to treat state "sales restrictions and purchase restrictions differently for pre-emption purposes" because the "right to sell federally approved [products] is meaningless in the absence of a purchaser's right to buy them"). There is no reason to reach a different result here.

B. The Stop-Selling Theory Thwarts The FDCA's Vesting Of Authority Over Interstate Pharmaceutical Marketing In FDA And Undermines The Statutory Protections Congress Granted Drug Manufacturers.

Beyond eviscerating Hatch-Waxman's central objective, the stop-selling theory fatally undermines the broader FDCA scheme. On one hand, it thwarts Congress's decision to vest FDA with authority to determine both when the scientific record is sufficient to permit the sale of drugs in interstate commerce and when that record requires that such products be withdrawn from interstate commerce. On the other hand, it undermines the specific statutory protections Congress gave manufacturers whose right to engage in interstate commerce might be affected by the exercise of that authority.

Indeed, the FDCA's long history evinces a clear intent to both centralize FDA control over the marketing of drugs in interstate commerce *and* to circumscribe the conditions under which FDA may order approved drugs withdrawn from interstate

commerce. To that end, the 1938 Act imposed strict federal approval requirements for drugs intended for interstate commercial sale, 1938 Act, § 505(b), 52 Stat. at 1052, and empowered FDA to suspend interstate sale approval in limited circumstances. *Id.* § 505(e), 52 Stat. at 1053. The 1962 Act went even further: It for the first time empowered FDA to consider drug effectiveness in exercising this authority, 1962 Act, § 102(c), 76 Stat. at 781, and expanded the range of conditions under which FDA could order approved drugs withdrawn from interstate commerce. *Id.* § 102(d), 76 Stat. at 782.

At each turn, Congress augmented the statutory protections for companies whose products were subject to FDA's continually expanding withdrawal authority. The 1938 Act granted manufacturers notice and hearing rights before an approval could be suspended; required FDA to memorialize its rationale for any suspension decision; and granted aggrieved parties the right to record-based judicial review of suspension decisions in federal district court. 1938 Act, §§ 505(e), (h), 52 Stat. at 1053. In 1962, Congress provided additional notice and hearing rights in cases where FDA was considering exercising its expanded withdrawal authority, 1962 Act, § 102(d), 76 Stat. at 782, and it transferred judicial review of withdrawal orders to the federal appellate courts. *Id.* § 104(d)(1), 76 Stat. at 784.

Hatch-Waxman ensured the same protections were available to generic manufacturers. *See* 21 U.S.C. §§ 355(e), (h) (requiring "due notice and opportunity for hearing to the applicant" whenever FDA seeks to "withdraw approval of an application *with respect to any drug under this section*" and

providing direct federal appellate review whenever FDA "withdraw[s] approval of *an application under this section*") (emphases added). Even more recently, Congress's 1997 amendments directed FDA to implement standards for "technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, … which shall apply equally to all individuals who review such applications." Food and Drug Administration Modernization Act of 1997, § 119(a), Pub. L. No. 105-115, 111 Stat. 2296, 2316 (codified at 21 U.S.C. § 355(b)(5)(A)) (NDAs); *id.* § 119(b), 111 Stat. at 2317-18 (codified at 21 U.S.C. § 355(j)(3)(A)) (ANDAs).

The stop-selling theory cannot be squared with this long history. It undercuts the statute's carefully circumscribed vesting of authority in FDA to control which drug designs can enter and remain in interstate commerce. *See, e.g.*, *Gross v. Pfizer, Inc.*, 825 F. Supp. 2d 654, 659 (D. Md. 2011) ("[A] state law duty that would compel generic manufacturers to stop production of a drug that under federal law they have the authority to produce … would directly conflict with the federal statutory scheme in which Congress vested sole authority with the FDA to determine whether a drug may be marketed in interstate commerce."); *see also Moore v. Mylan Inc.*, 840 F. Supp. 2d 1337, 1352 n.14 (N.D. Ga. 2012) ("[A]ny such state law duty [to withdraw a generic drug from interstate commerce] would directly conflict with the federal statutory scheme in which Congress vested sole authority with the FDA to determine whether a drug may be marketed in interstate commerce."); *Aucoin*, 2012 WL 2990697, at *9 (E.D. La. July 20, 2012) ("To require a generic

manufacturer to remove a drug from the market would repudiate … the FDA.").

Indeed, allowing lay juries to second-guess FDA's decision to maintain interstate marketing approval for certain drug designs strikes at the heart of Congress's decision to vest such authority in FDA. That delegation of authority reflects the principle that such decisions should be made in a systematic, evidence-based manner by an expert federal agency—not laypersons who lack the technical skill and experience of FDA's scientific experts in evaluating pharmaceutical designs. *See, e.g.*, *Riegel*, 552 U.S. at 325 ("[O]ne would think that tort law, applied by juries under a negligence or strict-liability standard, is [even] less deserving of preservation [than a] state statute, or a regulation adopted by a state agency, [which] could at least be expected to apply cost-benefit analysis similar to that applied by the experts at the FDA.… A jury, on the other hand, sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court."); *see also* Stephen Breyer, *Active Liberty: Interpreting Our Democratic Constitution* 102-03 (2005) ("Without delegation to experts, an inexpert public, possessing the will, would lack the way.").

That deliberate policy choice is clearly reflected in the 1997 amendments' requirement that FDA establish expertise-driven qualifications that "shall apply equally *to all individuals* who review [drug] applications." 21 U.S.C. § 355(b)(5)(A) (NDAs) (emphasis added); *id.* § 355(j)(3)(A)) (ANDAs). Needless to say, it is impossible to apply those congressionally required qualifications to lay jurors

that the stop-selling theory charges with reviewing whether a given drug design should remain approved for interstate commercial sale.

The same policy likewise is reflected in the laundry list of cases where federal courts have refused under *Chevron* to second-guess FDA's expert decisions governing the approval of drugs for sale in interstate commerce. *See, e.g.*, *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 766 (D.C. Cir. 2010) ("We are hard pressed to second-guess the FDA's view, especially since it rests on the agency's evaluation of scientific data within its area of expertise.") (quotation omitted); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998) ("FDA's 'judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.'") (quoting *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995)); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug…. We therefore defer to its reasonable findings."); *see also Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) ("Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background. The determination whether a drug is … safe and effective … necessarily implicates complex chemical and pharmacological considerations.") (quotation omitted).

The stop-selling theory also strips parties of the specific statutory protections federal law grants them before their products lawfully can be ordered withdrawn from interstate commerce. Again, those provisions explicitly require (among other things) the production of a written decision detailing the rationale for ordering FDA-approved drugs withdrawn from interstate commerce, 21 U.S.C. §§ 355(e), (g), and not only vest the federal appellate courts with exclusive jurisdiction and direct review authority over such decisions but declare that "[t]he finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive." *Id.* § 355(h). Without belaboring the point, state-law tort verdicts provide none of the specific protections that Congress repeatedly has extended to parties whose products effectively are being forced off the market.[11]

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[11] It is no answer that a civil trial arguably provides *similar* protections. As this Court repeatedly has explained, the means Congress has chosen are as important as the ends. *See, e.g.*, *Crosby v. National Foreign Trade Council*, 530 U.S. 363, 379 (2000) ("The fact of a common end hardly neutralizes conflicting means.") (citing *Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 103 (1992) (plurality opinion) ("'A state law also is pre-empted if it interferes with the methods by which the federal statute was designed to reach th[at] goal.'") (quoting *Ouellette*, 479 U.S. at 494, with alteration)); *MCI Telecomms. Corp. v. AT&T Co.*, 512 U.S. 218, 231 n.4 (1994) ("[W]e … are bound, not only by the ultimate purposes Congress has selected, but by the means it has deemed appropriate, and prescribed, for the pursuit of those purposes."); *see also Block v. Community Nutrition Inst.*, 467 U.S. 340, 349 (1984) ("[W]hen a statute provides a detailed mechanism for judicial consideration of particular issues at the behest of particular persons, judicial

C. *Wyeth* Is Not To The Contrary.

To its credit, the First Circuit conceded that the stop-selling theory undermines *both* Hatch-Waxman's core objectives *and* the FDCA's vesting in FDA of authority over the withdrawal of drugs from interstate commerce. PA10a ("There is no doubt that Congress wanted to reduce medical costs by spurring generic copycat drugs [and *Mensing*] held that Congress cannot have wanted the generic to pay damages under state law for a label that the FDA required.") (citing *inter alia* 21 U.S.C. § 355(j)(2)(A)); *id*. (acknowledging that the stop-selling theory requires "second-guessing the FDA"). Nonetheless, the appellate court once again thought it could evade those concessions by asserting that *Wyeth* "adopted a general no-preemption rule." PA11a.

As previously explained, that simply is not so. *Wyeth* did *not* involve generic drugs, so it had no occasion to address Hatch-Waxman's textually manifest goal of promoting the interstate commercial sale of generic drugs that share a previously approved drug design in order to reduce healthcare costs. *Mensing did* involve generic drugs, and it explained in no uncertain terms that Hatch-Waxman's "special, and different, regulation of generic drugs" fulfilled that evident legislative objective by "allow[ing] the generic drug market to expand, [and] bringing more drugs more quickly and cheaply to the public. [D]ifferent federal statutes

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review of those issues at the behest of other persons may be found to be impliedly precluded.").

and regulations may, as here, lead to different pre-emption results." 131 S. Ct. at 2582.

Nor did *Wyeth* reject the foregoing historical analysis of Congress's delegation of withdrawal authority to FDA or its repeated extension of legal protections to parties aggrieved by FDA's exercise of that authority. Once again, *Wyeth* had no occasion to consider those specific textual provisions because they were not remotely implicated by the plaintiff's claim that Wyeth should have changed its product labeling unilaterally—as the Court held federal regulations specifically authorized Wyeth to do. *Wyeth*, 555 U.S. at 568-69; *see also id*. at 575 ("Wyeth relies not on any statement by Congress, but instead on the preamble to a 2006 FDA regulation governing the content and format of prescription drug labels."). That is why the Court repeatedly characterized FDA's congressionally delegated authority over branded drug labeling standards as establishing only a "floor" and not also (as Wyeth contended) a "ceiling." *Id*. at 573, 575, 577. And it is why the Court ultimately held only that "Wyeth has not persuaded us *that failure-to-warn claims like Levine's* obstruct the federal regulation of drug labeling," 555 U.S. at 581—not that any conceivable state-law claim (however outlandish and whatever its subject matter) comports with the FDCA.[12]

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[12] Indeed, *Wyeth*'s core holding was merely that FDA's *regulatory preamble* did not preempt state law failure-to-warn claims; as the Court explained, that preamble was not "a specific agency regulation bearing the force of law" and did "not merit deference," *id*. at 580, because FDA previously "cast federal labeling standards as a floor upon which States could

Wyeth thus offers no support for the First Circuit's radical conclusion that state-law juries are free to supplant FDA's statutorily delegated authority over the approval and withdrawal of drug designs from interstate commerce—much less for its apparent belief that state-law juries are free to exercise such authority despite failing to provide the specific statutory protections Congress granted parties affected by the exercise of such authority. Again, it is undisputed that the federal labeling and design requirements for generic drugs set both a "floor" and a "ceiling," rendering *Wyeth*'s assertions regarding congressional intent in the branded labeling context beside the point. Indeed, had *Wyeth* intended to go any further, it would have been entirely unnecessary for the Court to consider (at great length) whether the federal labeling standards

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build and repeatedly disclaimed any attempt to pre-empt failure-to-warn claims." *Id.* at 577-78 (discussing FDA, *Prescription Drug Product Labeling; Medication Guide Requirements—Final Rule*, 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998)); *see also id.* at 582 (Breyer, J., concurring) (emphasizing "the Court's statement that we have no occasion in this case to consider the pre-emptive effect of a specific agency regulation bearing the force of law," noting that "state law will sometimes interfere with the FDA's desire to create a drug label containing a specific set of cautions and instructions," concluding "it is possible that such determinations would have pre-emptive effect," and reiterating that "such a regulation is not at issue in this case.") (internal citations and quotations omitted). Suffice it to say, Mutual's argument here is based on specific provisions of the FDCA that unquestionably bear the force of law, and FDA has *never* taken the position that federal design standards for generic drugs are merely a floor upon which the states are free to build.

were both a floor and a ceiling, and whether the CBE regulation did or did not permit Wyeth to change its product labeling without first securing FDA's prior approval; the simple (and far shorter) answer would have been that those questions were irrelevant because Wyeth could have pulled Phenergan® off the market if it wanted to avoid state tort liability.

At bottom, the sharp conflict between the stop-selling theory and Congress's textually evident purposes and objectives forecloses liability here.

CONCLUSION

The judgment should be reversed.

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Respectfully submitted,

JAY P. LEFKOWITZ, P.C.
Counsel of Record
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
(212) 446-4800
(212) 446-4900 (fax)
lefkowitz@kirkland.com

MICHAEL W. MCCONNELL
MICHAEL D. SHUMSKY
JOHN K. CRISHAM
KIRKLAND & ELLIS LLP
655 Fifteenth St., N.W.
Washington, DC 20005
(202) 879-5000
(202) 879-5200 (fax)
mcconne@kirkland.com
mshumsky@kirkland.com
jcrisham@kirkland.com

Counsel for Petitioner Mutual Pharmaceutical Company, Inc.

ADDENDUM A

United States Code Annotated

Title 21. Food and Drugs

Chapter 9. Federal Food, Drug and Cosmetics Act

Subchapter V. Drugs and Devices

Part A. Drugs and Devices

§ 355. New Drugs

Effective date: December 8, 2003

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(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. 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), and (G) any assessments required under section 355c of this title.

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which

information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the

notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice

An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice

A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of Title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of Title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary

and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of Title 42 (including all scientific and

medical matters, chemistry, manufacturing, and controls).

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the

holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted 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 the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(D) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was

dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall

review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of

reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three

years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability [FN1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the

approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(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.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that 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 labeling thereof; or (4) the patent information prescribed by

subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the

Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of

Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the

United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including—

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a

"clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that—

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefore, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to

whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

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

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a

petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(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;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed

(i) Agreement to give notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph—

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice

An applicant required under this subparagraph to give notice shall give notice to—

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by

the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice

A notice required under this subparagraph shall—

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence

studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection

(including scientific matters, chemistry, manufacturing, and controls).

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

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title, or no petition to file an application for the drug with the

different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient 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 paragraph (2)(A)(i) and that 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 such paragraph;

(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;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) of this section before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an

action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed—

(aa) if the judgment of the district court is appealed, the approval shall be made effective on—

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period

(I) Effectiveness of application

Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions

In this paragraph:

(aa) 180-day exclusivity period

The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) First applicant

As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application

As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval

(AA) In general

The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F)

or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation

A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(C) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of

the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period

(i) Definition of forfeiture event

In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market

The first applicant fails to market the drug by the later of—

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section.

(II) Withdrawal of application

The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification

The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval

The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements

for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner

The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of Title 15, except that the term includes section 45 of Title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents

All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture

The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant

If all first applicants forfeit the 180-day exclusivity period under clause (ii)—

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and

conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the

list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if—

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of—

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order

with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(l) Public disclosure of safety and effectiveness data

Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown—

(1) if no work is being or will be undertaken to have the application approved,

(2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(3) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(4) if the Secretary has determined that such drug is not a new drug, or

(5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

(m) "Patent" defined

For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

(n) Scientific advisory panels

(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of Title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of

the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel

essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member's own scientific work is involved.

(5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including travel-time, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of Title 5, for persons in the Government service employed intermittently.

(7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions

and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

CHAP. 3915. —*An Act* For preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That it shall be unlawful for any person to manufacture within any Territory or the District of Columbia any article of food or drug which is adulterated or misbranded, within the meaning of this Act; and any person who shall violate any of the provisions of this section shall be guilty of a misdemeanor, and for each offense shall, upon conviction thereof, be fined not to exceed five hundred dollars or shall be sentenced to one year's imprisonment, or both such fine and imprisonment, in the discretion of the court, and for each subsequent offense and conviction thereof shall be fined not less than one thousand dollars or sentenced to one year's imprisonment, or both such fine and imprisonment, in the discretion of the court.

SEC. 2. That the introduction into any State or Territory or the District of Columbia from any other State or Territory or the District of Columbia, or from any foreign country, or shipment to any foreign country of any article of food or drugs which is adulterated or misbranded, within the meaning of this Act, is hereby prohibited; and any person who shall

ship or deliver for shipment from any State or Territory or the District of Columbia to any other State or Territory or the District of Columbia, or to a foreign county, or who shall receive in any State or Territory or the District of Columbia from any other State or Territory or the District of Columbia, or foreign country, and having so received, shall deliver, in original unbroken packages, for pay or otherwise, or offer to deliver to any other person, any such article so adulterated or misbranded within the meaning of this Act, or any person who shall sell or offer for sale in the District of Columbia or the Territories of the United States any such adulterated or misbranded foods or drugs, or export or offer to export the same to any foreign country, shall be guilty of a misdemeanor, and for such offense be fined not exceeding two hundred dollars for the first offense, and upon conviction for each subsequent offense not exceeding three hundred dollars or be imprisoned not exceeding one year, or both, in the discretion of the court: *Provided*, That no article shall be deemed misbranded or adulterated within the provisions of this Act when intended for export to any foreign country and prepared or packed according to the specifications or directions of the foreign purchaser when no substance is used in the preparation or packing thereof in conflict with the laws of the foreign country to which said article is intended to be shipped; but if said article shall be in fact sold or offered for sale for domestic use or consumption, then this provision shall not exempt said article from the

operation of any of the other provisions of the Act.

* * *

SEC. 4. That the examinations of specimens of foods and drugs shall be made in the Bureau of Chemistry of the Department of Agriculture, or under the direction and supervision of such Bureau, for the purpose of determining from such examinations whether such articles are adulterated or misbranded within the meaning of this Act; and if it shall appear from any such examination that any of such specimens is adulterated or misbranded within the meaning of this Act, the Secretary of Agriculture shall cause notice thereof to be given to the party from whom such sample was obtained. Any party so notified shall be given an opportunity to be heard, under such rules and regulations as may be prescribed as aforesaid, and if it appears that any of the provisions for this Act have been violated by such party, then the Secretary of Agriculture shall at once certify the facts to the proper United States district attorney, with a copy of the results of the analysis or the examination of such article duly authenticated by the analyst or officer making such examination, under the oath of such officer. After judgment of the court, notice shall be given by publication in such manner as may be prescribed by the rules and regulations aforesaid.

SEC. 5. That is shall be the duty of each district attorney to whom the Secretary of Agriculture shall report any violation of this

Act, or to whom any health or food or drug officer or agent of any State, Territory, or the District of Columbia shall present satisfactory evidence of any such violation, to cause appropriate proceedings to be commenced and prosecuted in the proper courts of the United States, without delay, for the enforcement of the penalties as in such case herein provided.

* * *

SEC. 10. That any article of food, drug, or liquor that is adulterated or misbranded within the meaning of this Act, and is being transported from one Sate, Territory, District, or insular possession to another for sale, or, having been transported, remains unloaded, unsold, or in original unbroken packages, or if it be sold or offered for sale in the District of Columbia or the Territories, or insular possessions of the United States, or if it be imported from a foreign country for sale, or if it is intended for export to a foreign country, shall be liable to be proceeded against in any district court of the United States within the district where the same is found, and seized for confiscation by a process of libel for condemnation. And if such article is condemned as being adulterated or misbranded, or of a poisonous or deleterious character, within the meaning of this Act, the same shall be disposed of by destruction or sale, as the said court may direct, and the proceeds thereof, if sold, less the legal costs and charges, shall be paid into the Treasury of the United States, but such goods shall not be sold in any jurisdiction contrary to the provisions of this Act or the laws of that jurisdiction: *Provided, however*, That upon the

payment of the costs of such libel proceedings and the execution and delivery of a good and sufficient bond to the effect that such articles shall not be sold or otherwise disposed of contrary to the provisions of this Act, or the laws of any State, Territory, District, or insular possession, the court may by order direct that such articles be delivered to the owner thereof. The proceedings of such libel cases shall conform, as near as may be, to the proceedings in admiralty, except that either party may demand trial by jury of any issue of fact joined in any such case, and all such proceedings shall be at the suit of and in the name of the United States.

* * *

PUBLIC LAWS - CHS. 649, 653, 675 - JUNE 24, 25, 1938 [52 STAT.]

[CHAPTER 675]

AN ACT

To prohibit the movement in interstate commerce of adulterated and misbranded food, drugs, devices, and cosmetics, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

CHAPTER I - SHORT TITLE

SECTION 1. This Act may be cited as the Federal Food, Drug, and Cosmetic Act.

* * *

NEW DRUGS

SEC. 505 (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the

manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) An application provided for in subsection (b) shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application.

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), 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; or (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, he

shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

(e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or (2) that the application contains any untrue statement of a material fact. The order shall state the findings upon which it is based.

(f) An order refusing to permit an application with respect to any drug to become effective shall be revoked whenever the Secretary finds that the facts so require.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the department designated by the Secretary or (2) by mailing the order by registered mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing to permit the application to become effective, or suspending the effectiveness of the application. Such appeal shall be taken by filing in the district court of the United States within any district wherein such applicant resides or has his principal place of business, or in the District Court of the United States for the District of Columbia, within sixty days after the entry of such order, a written petition praying that

the order of the Secretary be set aside. A copy of such petition shall be forthwith served upon the Secretary, or upon any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court a transcript of the record upon which the order complained of was entered. Upon the filing of such transcript such court shall have exclusive jurisdiction to affirm or set aside such order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure to do so. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive and his recommendation, if any, for the setting aside of the original order. The judgment and decree of the court affirming or setting aside any such order of the Secretary shall be final, subject to review as provided in sections 128, 239, and 240 of the Judicial Code, as amended (U.S.C., 1934 ed., title 28, secs. 225, 346, and 347), and in section 7, as amended, of the Act

entitled "An Act to establish a Court of Appeals for the District of Columbia", approved February 9, 1893 (D.C. Code, title 18, sec. 26). The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

* * *

PUBLIC LAW 87-781 - OCT. 10, 1962 [76 STAT.]

Public Law 87-781

AN ACT

To protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs, authorize standardization of drug names, and clarify and strengthen existing inspection authority; and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act, divided into titles and sections according to the following table of contents, may be cited as the "Drug Amendments of 1962".

* * *

EFFECTIVENESS AND SAFETY OF NEW DRUGS

SEC. 102. (a) (1) Section 201 (p) (1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 (p)(1)), defining the term "new drug", is amended by (A) inserting therein, immediately after the words "to evaluate the safety", the words "and effectiveness", and (B) inserting therein, immediately after the words "as safe", the words "and effective".

(2) Section 201 (p)(2) of such Act (21 U.S.C. 321 (p)(2)) is amended by inserting therein, immediately after the word "safety", the words "and effectiveness".

(b) Section 505(b) of such Act (21 U.S.C. 355(b)) is amended by inserting therein, immediately after the words "is safe for use", the words "and whether such drug is effective in use".

(c) Section 505(d) of such Act (21 U.S.C. 355 (d)) is amended to read as follows:

"(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) 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), 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) 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), 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."

(d) Section 505(e) of such Act (21 U.S.C. 355(e)) is amended to read as follows:

"(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved,

evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that 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 labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated

together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packaging of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based."

* * *

NEW DRUG CLEARANCE PROCEDURE

SEC. 104. (a) Section 505(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(a)), is amended to read as follows:

"(a) No personal shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug."

(b) Section 505(c) of such Act (21 U.S.C. 355(c)) is amended to read as follows:

"(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either -

"(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

"(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs."

(c) Section 505(f) of such Act (21 U.S.C. 355 (f)) is amended to read as follows:

"(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, with-drawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate."

(d)(1) The first four sentences of section 505(h) of such Act (21 U.S.C. 355(h)) are amended to read as follows: "An appeal may be taken by the

applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order."

(2) The ninth sentence of such section 505(h) is amended to read as follows: "The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code."

* * *

PUBLIC LAW 98-417 - SEPT. 24, 1984

98 STAT. 1585

Public Law 98-417
98th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise the procedures for new drug applications, to amend title 35, United States Code, to authorize the extension of the patents for certain regulated products, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Drug Price Competition and Patent Term Restoration Act of 1984".

TITLE I – ABBREVIATED NEW DRUG APPLICATIONS

Sec. 101. Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by redesignating subsection (j) as subsection (k) and inserting after subsection (i) the following:

"(j)(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

"(2)(A) An abbreviated application for a new drug shall contain – "(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (6) (hereinafter in this subsection referred to as a 'listed drug');

"(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that

the active ingredient of the new drug is the same as that of the listed drug;

"(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

"(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 201(p), and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

"(iii) information to show that the route of administration, the dosage form, and strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

"(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clasue (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;

"(vi) the items specified in clauses (B) through (F) of subsection (b)(1);

"(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) –

"(I) that such patent information has not been filed,

"(II) that such patent has expired,

"(III) of the date on which such patent will expire, or

"(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

"(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a

use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

"(B)(i) An applicant who makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give the notice required by clause (ii) to—

"(I) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

"(II) the holder of the approved application under subsection (b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

"(ii) The notice referred to in clause (i) shall state that an application, which contains data from bioavailability or bioequivalence studies, has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of such drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

"(iii) If an application is amended to include a certification described in subparagraph (A)(vii)(IV), the notice required by clause (ii) shall be given when the amended application is submitted.

"(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds –

"(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

"(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

"(3) Subject to paragraph (4), the Secretary shall approve an application for a drug unless the Secretary finds –

"(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality and purity;

"(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

"(C)(i) if the listed drug has only one active ingredient, information submitted with the application

is insufficient to show that the active ingredient is the same as that of the listed drug;

"(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

"(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show –

"(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

"(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 201(p),

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

"(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage from, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

"(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage

form, or strength was approved under paragraph (2)(C);

"(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage from, or strength which is not the same;

"(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient 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 paragraph (2)(A)(i) and that 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 such paragraph;

"(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;

"(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or

(ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

"(I) the approval under subsection (c) of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e), the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) for grounds described in the first sentence of subsection (e), the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (5), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

"(J) the application does not meet any other requirement of paragraph (2)(A); or

"(K) the application contains an untrue statement of material fact.

"(4)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

"(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined under the following:

"(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

"(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

"(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that –

"(I) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of the court decision,

"(II) if before the expiration of such period the court decides that such patent has been infringed, the approval shall be made effective on such date as the court orders under section 271(e)(4)(A) of title 35, United States Code, or

"(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not

infringed, the approval shall be made effect on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (2)(B)(i) is received, no action may be brought under section 2201 of title 28, United States Code, for a declaratory judgment with respect to the patent. Any action brought under section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

"(iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing such a certification, the application shall be made effective not earlier than one hundred and eighty days after –

"(I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

"(II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier

"(C) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within

thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs

"(D)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

"(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains

a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

"(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of enactment of this subsection and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) for such drug.

"(iv) If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the

person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

"(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from the date of enactment of this subsection.

"(5) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended –

"(A) for the same period as the withdrawal or suspension under subsection (e) or this paragraph, or

"(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary

determines that the withdrawal from sale is not for safety or effectiveness reasons.

"(6)(A)(i) Within sixty days of the date of the enactment of this subsection, the Secretary shall publish and make available to the public –

"(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) before the date of the enactment of this subsection;

"(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

"(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

"(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) or approved under this subsection during the thirty-day period.

"(iii) When patent information submitted under subsection (b) or (c) respecting a drug included on the list is to be published by the Secretary the Secretary shall, in revisions made under clause (ii), include such information for such drug.

"(B) A drug approved for safety and effectiveness under subsection (c) or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or the date of enactment, whichever is later.

"(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under paragraph (5) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list –

"(i) for the same period as the withdrawal or suspension under subsection (e) or paragraph (5), or

"(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

"(7) For purpose of this subsection:

"(A) The term 'bioavailability' means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

"(B) A drug shall be considered to be bioequivalent to a listed drug if –

"(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

"(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.".

* * *

111 STAT. 2296 PUBLIC LAW 105-115 - NOV. 21, 1997

Public Law 105-115

105th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

* * *

SEC. 119. CONTENT AND REVIEW OF APPLICATIONS.

(a) Section 505(b).—Section 505(b) (21 U.S.C. 355(b)) is amended by adding at the end of the following:

"(4)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 351 of the Public Health Service Act, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

"(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of

an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

"C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

"(i) with the written agreement of the sponsor or applicant; or

"(ii) pursuant to a decision, made in accordance with the subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

"(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

"(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

"(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel nnless [sic] the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

"(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 351 of the Public Health Service Act (including all scientific and medical matters, chemistry, manufacturing, and controls.".

(b) Section 505(j).—

(1) Amendment.—Section 505(j) (21 U.S.C. 335(j)) is amended—

(A) by redesignating paragraphs (3) through (8) as paragraphs (4) through (9), respectively; and

(B) by adding after paragraph (2) the following:

"(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

"(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies.

Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

"(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

"(i) with the written agreement of the sponsor or applicant; or

"(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug ahs been identified after the testing has begun.

"(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

"(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

"(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing

division determines that a delay is necessary to assure the marketing of a safe and effective drug.

"(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).".

(2) Conforming Amendments.—Section 505(j) (21 U.S.C. 355(j)), as amended by paragraph (1), is further amended—

(A) in paragraph (2)(A)(i), by striking "(6)" and inserting "(7)";

(B) in paragraph (4) (as redesignated in paragraph (1)), by striking "(4)" and inserting "(5)";

(C) in paragraph (4)(l) (as redesignated in paragraph (1)), by striking "(5)" and inserting "(6)"; and

(D) in paragraph (7)(C) (as redesignated in paragraph (1)), by striking "(5)" each place it occurs and inserting "(6)".

* * *

ADDENDUM B

States That Apply Restatement (Second) of Torts § 402A, cmt. k

Ala.	*Stone v. Smith, Kline & French Labs.*, 447 So. 2d 1301 (Ala. 1984)
Ariz.	*Gaston v. Hunter*, 588 P.2d 326 (Ariz. Ct. App. 1978)
Ark.	*West v. Searle & Co.*, 806 S.W.2d 608 (Ark. 1991)
Cal.	*Brown v. Superior Court*, 751 P.2d 470 (Cal. 1988)
Colo.	*Ortho Pharm. Corp. v. Heath*, 722 P.2d 410 (Colo. 1986) (en banc), *overruled on other grounds by Armentrout v. FMC Corp.*, 842 P.2d 175 (Colo. 1992) (en banc)
Conn.	*Hurley v. Heart Physicians, P.C.*, 898 A.2d 777 (Conn. 2006)
D.C.	*Fisher v. Sibley Mem'l Hosp.*, 403 A.2d 1130 (D.C. 1979)
Fla.	*Adams v. G.D. Searle & Co., Inc.*, 576 So. 2d 728 (Fla. Ct. App. 1991)
Ga.	*Bryant v. Hoffmann-La Roche, Inc.*, 585 S.E.2d 723 (Ga. App. 2003)
Haw.	*Larsen v. Pacesetter Sys., Inc.*, 837 P.2d 1273 (Haw. 1992)
Ill.	*Woodill v. Parke Davis & Co.*, 402 N.E.2d 194 (Ill. 1980)
Ind.	*Ortho Pharm. Corp. v. Chapman*, 388 N.E.2d 541 (Ind. Ct. App. 1979)
Iowa	*Moore v. Vanderloo*, 386 N.W.2d 108 (Iowa 1986)

Kan.	*Savina v. Sterling Drug, Inc.*, 795 P.2d 915 (Kan. 1990)
Ky.	*Larkin v. Pfizer, Inc.*, 153 S.W.3d 758 (Ky. 2004)
La.	*Kinney v. Hutchinson*, 468 So. 2d 714 (La. Ct. App. 1985)
Md.	*Fellows v. USV Pharm. Corp.*, 502 F. Supp. 297 (D. Md. 1980)
Mass.	*Lareau v. Page*, 840 F. Supp. 920 (D. Mass. 1993)
Mich.	*Nichols v. McNeilab, Inc.*, 850 F. Supp. 562 (E.D. Mich. 1993)
Minn.	*Kociemba v. G.D. Searle & Co.*, 680 F. Supp. 1293 (D. Minn. 1988)
Miss.	*Bennett v. Madakasira*, 821 So. 2d 794 (Miss. 2002), *overruled on other grounds by Bennett v. Madakasira*, 821 So. 2d 794 (Miss. 2002)
Mo.	*Pollard v. Ashby*, 793 S.W.2d 394 (Mo. Ct. App. 1990)
Neb.	*Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827 (Neb. 2000)
N.J.	N.J.S.A. §2A:58C-3(a)(3)
N.M.	*Davila v. Bodelson*, 704 P.2d 1119 (N.M. Ct. App. 1985)
N.Y.	*Martin v. Hacker*, 628 N.E.2d 1308 (N.Y. 1993)
N.C.	N.C. Gen. Stat. § 99B-6(d)
Ohio	Ohio Rev. Code Ann. § 2307.75(D)

Okla.	*Tansy v. Dacomed Corp.*, 890 P.2d 881 (Okla. 1994)
Or.	Or. Rev. Stat. § 30.920(3)
Pa.	*Lance v. Wyeth*, 4 A.3d 160 (Pa. Super. Ct. 2010)
R.I.	*Castrignano v. E.R. Squibb & Sons, Inc.*, 546 A.2d 775 (R.I. 1988)
S.C.	S.C. Code Ann. § 15-73-30
S.D.	*McElhaney v. Eli Lilly & Co.*, 575 F. Supp. 228 (D.S.D. 1983)
Tenn.	*Rodriguez v. Stryker Corp.*, No. 2:08-0124, 2011 WL 31462 (M.D. Tenn. Jan. 5, 2011)
Tex.	*Hackett v. G.D. Searle & Co.*, 246 F. Supp. 2d 591 (W.D. Tex. 2002)
Utah	*Grundberg v. Upjohn Co.*, 813 P.2d 89 (Utah 1991)
Wash.	*Young v. Key Pharm., Inc.*, 922 P.2d 59 (Wash. 1996).
Wyo.	*Jacobs v. Dista Prods. Co.*, 693 F. Supp. 1029 (D. Wyo. 1988)