NO. 14-1522 (L)

United States Court of Appeals

for the

Fourth Circuit

MYLAN PHARMACEUTICALS INC.,
WATSON LABORATORIES, INC.,
and
LUPIN PHARMACEUTICALS, INC.

Plaintiffs-Appellants

– v. –

U.S. FOOD AND DRUG ADMINISTRATION
and
TEVA PHARMACEUTICALS USA, INC.

Defendants-Appellees

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR
THE NORTHERN DISTRICT OF WEST VIRGINIA AT CLARKSBURG

BRIEF OF APPELLANTS MYLAN PHARMACEUTICALS INC. AND WATSON LABORATORIES, INC.

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RULE 26.1 CORPORATE DISCLOSURE STATEMENT

Mylan and Watson respectfully submit the following disclosure required by Fed. R. App. P. 26.1:

1. Mylan Pharmaceuticals Inc. is a wholly owned subsidiary of Mylan Inc., a publicly held company whose stock is traded on NASDAQ under the symbol "MYL."
2. Mylan Pharmaceuticals Inc. is a pharmaceutical company specializing in the development, manufacture, and marketing of affordable generic medicines.
3. Watson Laboratories, Inc. is a wholly owned subsidiary of Actavis plc, a publicly held company whose stock is traded on NYSE under the symbol "ACT."
4. Watson Laboratories, Inc. is a pharmaceutical company focused on developing and manufacturing generic drug products.

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JURISDICTIONAL STATEMENT

This action for declaratory and injunctive relief arises under the FDC Act, 21 U.S.C. §§ 301-397; and the Administrative Procedure Act, 5 U.S.C. §§ 551-706. The District Court had subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1361. This Court has jurisdiction under 28 U.S.C. §§ 1291 and 1292, because the District Court entered a final judgment, in addition to an interlocutory order denying a preliminary injunction.

The District Court's memorandum opinion and order denying Mylan's motion for preliminary injunction was entered on May 29, 2014. Mylan timely filed its notice of appeal on May 30, 2014. Lupin filed its notice of appeal of the order denying the preliminary injunction on June 3, 2014. The District Court entered a final judgment on June 16, 2014. Mylan timely filed its notice of appeal of the final judgment on June 16, 2014. Lupin timely filed a notice of appeal of the final judgment on July 2, 2014. Watson filed a notice of appeal of both orders on June 16, 2014. Thus, appeals of both District Court decisions are timely.

REPRODUCTION OF STATUTORY AND REGULATORY PROVISIONS

The statutory sections at issue in this case are reproduced in an Addendum to this brief.

SUMMARY OF THE CASE

The U.S. Food and Drug Administration ("FDA"), in its April 24, 2014 Decision underlying this litigation (the "FDA Decision"), ignored the plain statutory language of the Hatch-Waxman Amendments governing the 180-day marketing exclusivity period for generic drug manufacturers. Congress specifically provided that a court decision finding a patent invalid triggers the running of the exclusivity period relating to that patent, which courts have described as the "court decision trigger." The FDA Decision, however, contravened the clear statutory language and invented an exception to the court decision trigger by creating ambiguity where none existed, denying multiple generic drug manufacturers the opportunity to distribute generic versions of one of the highest-grossing drugs currently available. The District Court upheld the FDA Decision. FDA – and the District Court – should be reversed.

Specifically, Congress provided that a court decision finding a patent invalid triggers the running of the generic drug marketing exclusivity period relating to that patent. The relevant statutory provision of the Hatch-Waxman Amendments[1] states that the period of 180-day marketing exclusivity for a generic drug begins running on:

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[1] The Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

> (II) the date of a decision of a court in [relevant patent litigation] holding the patent which is the subject of the certification to be invalid or not infringed . . . .

Federal Food, Drug, and Cosmetic Act ("FDC Act") § 505(j)(5)(B)(iv)(II), 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2002); Addendum. There are no statutory exceptions to this provision. Yet, the FDA Decision ignored this clear statutory language and unlawfully invented an exception from the court decision trigger for a "patent which is the subject of the certification" if that patent – an original patent – is later reissued, even when the exclusivity period attributable to the original patent expired more than five years before issuance of the reissue patent. FDA reached its decision by altering the clear statutory language defining the date when a generic drug marketing exclusivity period begins to run.

When FDA tried in the past to change the legal requirements for generic drug marketing exclusivity periods, courts, including this Court, reversed FDA.[2] The Court should do the same in this case.

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[2] *Inwood Labs., Inc. v. Young*, 723 F. Supp. 1523, 1526 (D.D.C.), *vacated as moot*, 43 F.3d 712 (D.C. Cir. 1989) (court rejected FDA attempt to add requirement that generic drug company could earn generic drug marketing exclusivity period only if sued by patent holder); *Mova Pharm.Corp. v. Shalala*, 955 F. Supp. 128, 130 (D.D.C. 1997), *aff'd*, 140 F.3d 1060 (D.C. Cir. 1998) (rejecting FDA attempt to read "successful defense" requirement into same provision); *accord Granutec, Inc. v. Shalala*, 139 F.3d 889 (4th Cir. 1998).

This case concerns the right to market generic versions of Celebrex®, a drug used for treatment of arthritis that has been sold by Pfizer Inc. ("Pfizer") for more than 16 years, with total 2013 U.S. sales of more than $2 billion. Complaint at 9, Watson Intervenor Complaint at 10; J.A. 26, 127. The effect of the FDA Decision was that FDA refused to grant final approval on May 30, 2014 to generic drug manufacturers other than Defendant-Appellee Teva Pharmaceuticals, Inc. ("Teva") for their generic versions of Celebrex®.

The FDA Decision held that Teva's 180-day marketing exclusivity period tied to an original patent for Celebrex® did not begin to run in 2008, despite FDA's admission that the patent was invalidated by a final court decision in 2008. Thus, FDA determined that Teva's exclusivity period blocked approvals for any other manufacturers of the generic version of Celebrex®. As a result, and because Teva entered into an agreement with Pfizer that settled their patent litigation and restricted Teva's ability to begin marketing the drug, consumers remain unable to obtain lower-priced generic versions of this important drug.

The FDA Decision unlawfully determined that Teva's 180-day marketing exclusivity period had not expired, even though it started running – and should have expired – in 2008, because of the final court decision holding the relevant patent invalid. The District Court refused to reverse the FDA Decision, erroneously construing the clear statutory definition of the court decision trigger,

despite ruling that "it appears that *Congress was referring* only *to original*, and not all, *patents when it drafted the court decision trigger clause.*" J.A. 272 (emphasis added). That finding by the District Court is fundamentally inconsistent with its ultimate holding that a final court decision invalidating the original patent did not operate as a court decision trigger.

Thus, on May 30, 2014, only Teva received final FDA approval to market the relevant dosage strengths of its generic version of Celebrex®. Pfizer's patent litigation settlement with Teva prohibits Teva from launching its generic product until December 2014, or earlier under certain circumstances. And the FDA Decision, upheld by the District Court, prevents any other manufacturer from marketing a generic version of the drug until 180 days after Teva begins commercial marketing. Consequently, absent action by this Court, no other generic drug manufacturers – including Plaintiff-Appellant Mylan Pharmaceuticals Inc. ("Mylan"); Appellant Watson Laboratories, Inc. ("Watson"), which intervened as a plaintiff in the District Court; and Appellant Lupin Pharmaceuticals, Inc. ("Lupin"), which also intervened as a plaintiff in the District Court – will likely receive FDA final approval for the relevant dosage strengths of their generic versions of Celebrex® until June 2015.

In erroneously granting a period of 180-day exclusivity to Teva, FDA, and then the District Court, also denied Mylan, Watson, and Teva their statutory right

to a *shared* period of 180-day exclusivity tied to the reissue patent for Celebrex®. This denial – which presents a separate and distinct issue from whether Teva's period of exclusivity tied to the original patent expired in 2008 – directly conflicts with the statutory framework, and is unlawful, arbitrary, and capricious.

Both parts of the FDA Decision should be reversed, as should the District Court ruling upholding the FDA Decision.

STATEMENT OF ISSUES

1. Whether the FDA Decision was unlawful, arbitrary, and capricious because it determined, contrary to the clear statutory language of the Hatch-Waxman Amendments, that a final court decision invalidating an original patent is not a court decision trigger for 180-day generic drug marketing exclusivity if the invalid patent is later replaced by a reissue patent.
2. Whether the FDA Decision to deny eligible generic drug manufacturing companies a period of shared exclusivity tied to the reissue patent was arbitrary, capricious, or otherwise not in accordance with law.

STATEMENT OF THE CASE

Mylan brought this action in the United States District Court for the Northern District of West Virginia immediately following issuance of the FDA Decision, and Watson and Lupin timely intervened. Mylan, joined by Watson, sought judicial review of the FDA Decision that adopted an unauthorized

interpretation of the court decision trigger in the FDC Act. Mylan moved immediately for a preliminary injunction, a motion that Watson and Lupin joined, to enjoin operation of the FDA Decision pending full judicial review, because Mylan would be irreparably harmed if the FDA Decision were to remain in effect beyond May 30, 2014. The District Court denied the preliminary injunction. The District Court then converted its ruling on the merits of Mylan's preliminary injunction motion to a final judgment on June 16, 2014. Both decisions have been appealed, and the appeals are consolidated in this Court.

STATEMENT OF FACTS

I. STATUTORY BACKGROUND

The FDA Decision interprets provisions of the FDC Act, which, as amended by the Hatch-Waxman Amendments, govern the approval of generic drugs. *See* FDC Act § 505, 21 U.S.C. § 355 *et seq*. Pioneer, or brand, companies file a New Drug Application ("NDA") for FDA approval to market a new drug product, and NDAs contain evidence of clinical testing establishing the safety and efficacy of the drug. FDC Act § 505(b), 21 U.S.C. § 355(b). Generic drug companies are permitted to market the generic version of a drug that was the subject of an NDA approval – after relevant patent protections have expired or have been successfully challenged – by filing an Abbreviated New Drug Application ("ANDA") that establishes bioequivalence to the NDA drug, which is referred to as the "Reference

Listed Drug." 21 C.F.R. § 314.3 (2013). The FDC Act provides that, under certain conditions, an ANDA applicant is entitled to a 180-day period during which FDA cannot approve ANDAs of subsequent applicants for the same drug. FDC Act § 505(j)(5)(B)(iv)(I)-(II), 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002).[3] This is commonly referred to as "180-day exclusivity." The statutory preconditions for 180-day exclusivity include the following:

1. The holder of an NDA for a brand drug, like Celebrex®, is required to submit to FDA for listing in the publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") "the patent number and the expiration date of *any patent*" that covers the brand drug or a method of using that drug. FDC Act § 505(b)(1)(G), 21 U.S.C. § 355(b)(1)(G) (emphasis added).

2. An ANDA applicant is required to submit one of four types of certifications (or a statement) to "*each patent*" listed in the Orange Book for the brand drug, one of which certifies that the patent in question is "invalid or will not be infringed" (a "Paragraph IV" certification). FDC Act § 505(j)(2)(A)(vii), 21

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[3] As the parties and the District Court agree, exclusivity periods for celecoxib (the active ingredient in Celebrex® and the name for the generic version of the drug) are governed by the version of the FDC Act in effect prior to enactment of the Medicare Prescription Drug, Improvement, and Modernization Act, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("MMA"), because the first ANDA for celecoxib with a Paragraph IV certification was submitted to FDA prior to the December 8, 2003 enactment of the MMA. FDC Act § 505(j)(5)(B)(iv)(I)-(II), 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002). The FDA Decision acknowledges this, as does the District Court decision. *See* FDA Decision at 3, Slip Op. at 5-6 n.2; J.A. 43, 255-56. The text of Section 505 prior to the MMA is reproduced in the Addendum. Unless otherwise noted, all FDC Act citations herein are to the pre-MMA version of the statute.

> U.S.C. § 355(j)(2)(A)(vii) (emphasis added). The submission of a Paragraph IV certification is capable of forming, and often does form, the basis for patent infringement litigation between the ANDA applicant and the patent holder. *See* FDC Act § 505(j)(2)(B), 21 U.S.C. § 355(j)(2)(B).

3. If the ANDA applicant is the first to submit a Paragraph IV certification to the particular patent, it becomes a so-called "first-filer" for purposes of 180-day exclusivity. FDC Act § 505(j)(5)(B)(iv)(I)-(II), 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002). If multiple applicants submit ANDAs containing Paragraph IV certifications on the same day, 180-day exclusivity can be shared.[4]

The specific statutory provision at issue in this case governs the commencement of the 180-day period of marketing exclusivity to which an ANDA applicant is entitled provided that the above conditions are met, i.e., (1) the patent has been listed in the Orange Book; (2) the ANDA applicant filed a Paragraph IV certification to that patent and notified the patent holder and NDA holder of the certification; and (3) the ANDA applicant was the first to file a Paragraph IV certification to that patent. In such circumstances, the statute provides that the 180-day exclusivity period begins to run (or is "triggered") on:

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[4] This "shared exclusivity" policy is articulated in FDA guidance. *See* FDA, Guidance for Industry, 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day, at 4-5 (July 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072851.pdf.

> (I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application,[5] 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, [6]
>
> whichever is earlier.

FDC Act § 505(j)(5)(B)(iv)(I)-(II), 21 U.S.C. § 355(j)(5)(B)(iv) (2002); Addendum. In other words, the 180-day marketing exclusivity period awarded to a company that was the "first-filer" begins to run when the first-filer commences commercial marketing of the drug (the commercial marketing trigger) or when the patent subject to the certification is held invalid or not infringed (the court decision trigger), whichever occurs first.

An ANDA applicant that is the first to file a Paragraph IV certification to a patent, thereby creating the basis for a period of 180-day exclusivity tied to that

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[5] The "trigger" in this subparagraph is referred to as the "commercial marketing trigger," which occurs if the first-filer (described in the subparagraph as the "applicant under the previous application") begins marketing the generic version of the drug. If commercial marketing begins prior to a "court decision trigger," the 180-day marketing exclusivity period begins to run on the date that commercial marketing begins.

[6] Throughout this brief, quotations from this subparagraph, defining the court decision trigger, generally replace the phrase "an action described in clause (iii)" with the phrase "relevant patent litigation." The "action" described is patent litigation between an ANDA holder and the patent holder or NDA filer and is based on the ANDA holder's Paragraph IV certification that the patent is invalid or not infringed.

patent, must "clear the patent thicket" entirely in order to take advantage of its statutory boon. Thus, if a first-filer to a particular patent wins a court decision declaring that patent invalid, unenforceable, or not infringed, but fails to win a comparable decision as to other patents covering the drug, it cannot market the generic version of the drug during the period of exclusivity tied to the patent that was declared invalid, because the other patents still apply to block marketing. No provision of the statute precludes such a result, and, indeed, it is not unusual for a marketing exclusivity period to expire before first-filers are able to market the drug. *See, e.g.*, *Hi-Tech Pharmacal Co., Inc. v. FDA*, 587 F. Supp. 2d 1, 4 (D.D.C. 2008); *Nostrum Pharms., LLC v. FDA*, No. 11-3111, 2011 WL 2652147, at *3 (D.N.J. July 6, 2011) (court upheld FDA's decision that the exclusivity period for Nostrum on one patent had expired, but Nostrum had obtained a separate and distinct exclusivity period for a different patent); *see also* Enoxaparin Sodium Injection, Approval Letter, ANDA 077857 (July 23, 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/077857s000ltr.pdf. With regard to enoxaparin sodium, a court decision triggered the exclusivity period for enoxaparin sodium injection, but the holder (or holders) of that exclusivity period was unable to market because it had not yet obtained FDA approval. The exclusivity expired, and the ANDA of a different company, Sandoz Inc., was approved first.

The relevant original patent for Celebrex®, U.S. Patent No. 5,760,068 ("the '068 patent"), was reissued on March 5, 2013, as U.S. Patent No. RE 44,048 ("the '048 patent"). Reissue patents are a subcategory of patents under U.S. patent law. A reissue patent is issued by the United States Patent and Trademark Office ("PTO") upon submission of a new and amended patent application when the original patent is "deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent . . . ." 35 U.S.C. § 251(a). A patent holder must surrender the predecessor patent as a condition of obtaining a reissue patent. *Id.*; 37 C.F.R. § 1.178(a). Once a reissue patent is issued for a drug that is the subject of an NDA, the NDA holder must list the patent in the Orange Book, as FDA concedes (FDA Decision at 4-5; J.A. 44-45, discussed further below). Also, once the reissue patent is published in the Orange Book, all ANDA applicants must file a certification to that patent (or a statement) under the Hatch-Waxman Amendments, just as they must for any other patent.

II. FACTUAL BACKGROUND

The FDA Decision addressed the statutory provisions governing both the creation of 180-day exclusivity, and the triggering and expiration of such exclusivity under the following factual circumstances:

1. Teva certified in its ANDA for celecoxib that a patent covering that drug, the '068 patent,[7] was invalid or not infringed, pursuant to the FDC Act, and Teva was the first filer to certify to that patent (Complaint at 10, FDA Decision at 1; J.A. 27, 41);

2. Teva was challenged in litigation by the patent-holder (G.D. Searle, which was acquired by Pfizer), and the U.S. Court of Appeals for the Federal Circuit held that the '068 patent was invalid, with a mandate that issued on May 13, 2008 (Complaint at 10-11, FDA Decision at 1; J.A. 27-28, 41);

3. Teva was not able to market its product following the court mandate on the '068 patent because the Federal Circuit held that two other patents listed in the Orange Book for Celebrex®, U.S. Patent Nos. 5,466,823 ("the '823 patent") and 5,563,165 ("the '165 patent"), were valid and infringed by Teva; thus, Teva failed to "clear the patent thicket" (*id*.);

4. On September 5, 2008, four months after the Federal Circuit's mandate invalidating the '068 patent, Pfizer submitted the '068 patent to the PTO for reissue proceedings (Watson Intervenor Complaint at 3; J.A. 120)

5. Nearly five years after the Federal Circuit's mandate on the '068 patent, on March 5, 2013, the PTO issued a reissue patent,the '048 patent, replacing the '068 patent (Complaint at 12, FDA Decision at 1; J.A. 29, 41); and

6. Teva and several other companies, including Mylan and Watson, first-filed Paragraph IV certifications to the '048 reissue patent, and were challenged in litigation by the patent holder in the U.S. District Court for the Eastern District of Virginia (Complaint at 12-14, FDA

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[7] A copy of the patent is available here: http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5,760,068.PN.&OS=PN/5,760,068&RS=PN/5,760,068.

Decision at 1, Watson Intervenor Complaint at 3; J.A. 29-30, 41, 120); that litigation resulted in the District Court invalidating the patent, but that decision was appealed, is therefore not final, and does not qualify as a court decision trigger (Complaint at 13, FDA Decision at 1; J.A. 30, 41).

The FDA Decision interpreted the FDC Act as follows:

- "[S]ection 505 of the FD&C Act [providing that the exclusivity period is to run as of 'the date of a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed'] is silent as to the effect of reissued patents on 180-day exclusivity." FDA Decision at 9; J.A. 49.

- "We conclude that the 'court-decision-trigger' provision of section 505(j)(5)(B)(iv) is ambiguous regarding a scenario in which an ANDA applicant makes a paragraph IV certification to an original patent, a court finds the patent invalid, and the [PTO] reissues the patent before any other [ANDA] applicant [has obtained final FDA approval]. In these circumstances, the statute is ambiguous regarding whether such a court decision should be considered to hold 'the patent which is the subject of the certification to be invalid or not infringed.'" FDA Decision at 10; J.A. 50 (citing FDC Act § 505(j)(5)(B)(iv), 21 U.S.C. § 355(j)(5)(B)(iv) (2002)).

- Under Section 505, FDA will treat "an original and reissued patent as a single 'bundle' of rights for purposes of 180-day exclusivity." FDA Decision at 9; J.A. 49.

- In light of the statute's purported ambiguity, "we believe that when a paragraph IV certification has been made to an original patent, subsequent paragraph IV certifications to a reissued patent that references the original patent should not be the basis for [a] separate period []of 180-day exclusivity." *Id*.

Based on these statutory interpretations, FDA granted Teva 180-day exclusivity to market generic celecoxib stemming from Teva's having filed the first Paragraph IV certification to the '068 patent. *Id*. ("eligibility for 180-day exclusivity would

remain intact for the first applicant on the original patent."). FDA acknowledges, however, that the May 13, 2008 Federal Circuit mandate would have caused Teva's exclusivity to expire in November 2008 were it not for the issuance of the '048 reissue patent nearly five years later. *See* FDA Decision at 1 n.1, Prelim. Inj. Hearing Transcript at 60; J.A. 41, 200. Nevertheless, FDA denied final approval to all ANDA applicants other than Teva. FDA also denied Mylan and Watson, as first-filers to the '048 reissue patent, a period of 180-day exclusivity tied to the '048 patent, which the two companies would have shared with Teva, because Teva also qualified as a first-filer to the '068 patent. Complaint at 11; J.A. 28.

On May 30, 2014, consistent with the FDA Decision, FDA issued a final approval to Teva for the relevant strengths of celecoxib, but informed Mylan and Watson that their final approvals were being withheld because of the exclusivity period, which was granted to Teva. *See* Mylan Mot. Expedited Briefing, Ex. 3 (D.I. 19). The immediate practical effect of the FDA Decision is to prevent these other ANDA applicants from entering the market for six months, if not more. In all likelihood, because of a settlement agreement between the brand drug manufacturer and Teva, the FDA Decision will delay Mylan and Watson, and

perhaps others, including Lupin, from receiving FDA final approvals to market generic celecoxib for nearly a year.[8]

SUMMARY OF ARGUMENT

This appeal presents two separate and distinct questions. The first is whether the Teva exclusivity period tied to the '068 patent expired in 2008. It did. Once this first question is answered in the affirmative, the second question is whether the first-filers to the '048 patent (which include Teva) are entitled to a shared period of exclusivity tied to the '048 patent. They are.

The FDA Decision, upheld by the District Court, unlawfully disregarded clear statutory language in determining that Teva's exclusivity period with respect to the '068 patent did not expire 180 days after the court decision trigger occurred in May 2008. Both FDA and the District Court found the statutory language defining the court decision trigger to be ambiguous. However, there is nothing ambiguous about the statute. When the Federal Circuit issued its May 2008 mandate holding the '068 patent invalid, the clear statutory language directed that Teva's exclusivity period tied to the '068 patent began to run and expired 180 days

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[8] If this Court determines that Teva's period of exclusivity tied to the '068 patent has in fact expired, and also decides that Mylan, Watson, and Teva share a period of exclusivity tied to the '048 patent, Lupin would be delayed from entering the market for an additional 180 days.

later, which was nearly six years ago. "Where the 'intent of Congress is clear … the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.'" *Chevron U.S.A., Inc. v. Nat. Res. Def. Council*, 467 U.S. 837, 842-43 (1984). The District Court even recognized that the court decision trigger refers to a court decision affecting the original patent – not the reissue patent – yet inexplicably disregarded this clear statutory language and its own analysis of this point. The District Court stated that, whatever the rule for other patents, using traditional tools of statutory interpretation, "it appears that Congress was referring only to original, and not all, patents when it drafted the court decision trigger clause." J.A. 272. Under *Chevron* Step One, this Court need look no further than the plain statutory language.

Even if this Court determines that the statutory language is unclear, which it is not, and the Court thus engages in review of the FDA Decision under what courts have referred to as *Chevron* "Step Two," FDA's reading of the statutory language must be rejected because it produces the absurd result that competing drug manufacturers can never know whether the exclusivity period has expired, given that a reissue patent could conceivably be granted at any time. *Chevron*, 467 U.S. 842-43. Similarly, FDA's "bundle of rights" approach produces the absurd and logically inconsistent result that a 180-day exclusivity period is transferred from an original to a reissue patent, while the triggering and expiration of that

same period do *not* carry forward. The FDA Decision is thus based on an unreasonable interpretation of the statutory language and must be rejected for that reason, as well.

The second question presented by this case is whether the first-filers to the '048 patent – believed to include Mylan, Watson, and Teva – are entitled to a shared exclusivity period tied to that patent, because Teva's original exclusivity period tied to the '068 patent has expired and the '048 patent is a new and distinct patent. Such an exclusivity period should be awarded to Mylan, Watson, and Teva because the statutory framework compels that result. Moreover, maintaining a separate exclusivity period for the first-filers to the reissue patent is the only reading of the statute consistent with the purposes of the Hatch-Waxman Amendments.[9]

ARGUMENT

I. STANDARD OF REVIEW

Because the issues on appeal are limited to the legal conclusions in the District Court order denying the preliminary injunction and the Final Judgment, the standard of review here is de novo. *See Stone v. Instrumentation Lab.Co.*, 591

[9] Appellant Lupin is filing a separate brief arguing that first-filers to the '048 patent are not entitled to shared 180-day exclusivity.

F.3d 239, 242-43 (4th Cir. 2009) ("a question of statutory interpretation . . . is a question of law that we review *de novo*"); *W.V. Ass'n. of Club Owners & Fraternal Servs., Inc. v. Musgrave*, 553 F.3d 292, 298 (4th Cir. 2009) (legal conclusions in preliminary injunction decision are reviewed de novo).

II. FDA'S DECISION TO AWARD TEVA A REVIVED PERIOD OF 180-DAY EXCLUSIVITY CONTRAVENES THE CLEAR STATUTORY LANGUAGE, AND IS UNREASONABLE, ARBITRARY, AND CAPRICIOUS.

A. The Statute Unambiguously Forecloses FDA's Interpretation of the "Court Decision Trigger."

The statutory provision at issue mandates that a 180-day exclusivity period is triggered by a "decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed." FDC Act § 505(j)(5)(B)(iv)(II), 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2002).

Agency actions are reviewed under the Administrative Procedure Act ("APA"). *See Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083-84 (D.C. Cir. 2001). Under the APA, a court is directed to "hold unlawful and set aside agency action" that it finds to be (1) in excess of statutory jurisdiction or (2) arbitrary and capricious. 5 U.S.C. § 706(2)(A), (C). In determining whether an agency's interpretation is in excess of statutory jurisdiction, the Court must employ the two-step analysis of *Chevron*. At *Chevron* Step One, the Court must look to the plain language of the relevant statute and exhaust "the 'traditional tools of statutory construction'" to ascertain Congressional intent. *Chamber of Commerce*

of U.S. v. N.L.R.B., 721 F.3d 152 (4th Cir. 2013) (quoting *Chevron*, 467 U.S. at 842 n.9). Thus, the Court must give effect to each word and clause of the statutory provision, in context, to determine whether the statute unambiguously forecloses FDA's interpretation. *See Shipbuilders Council of Am. v. U.S. Coast Guard*, 578 F.3d 234, 244-45 (4th Cir. 2009) ("we have a duty, where possible, to give effect to all operative portions of the enacted language, including its every clause and word" (internal quotations omitted)); *Chamber of Commerce*, 721 F.3d at 162 ("in addition to the language of the [statutory provision] itself, we must look to the specific context in which that language is used, and the broader context of the statute as a whole" (internal quotations omitted)).

Within the statutory context – and giving effect to each word as written – the plain meaning of the court decision trigger admits no ambiguity. The statute expressly forecloses FDA's position. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43.[10]

[10] FDA's analysis of the court decision trigger language is found at pages 9-11 of the FDA Decision. J.A. 49-51.

1. The Plain Meaning and Statutory Context Dictate that the Court Decision Trigger Must Apply to the Federal Circuit's 2008 Mandate.

As detailed in the Statutory Background section, the court decision trigger is the final step in a series of linked statutory provisions that create and define 180-day exclusivity periods. Each of these statutory provisions is tied to a certification that is, in turn, tied to a patent. There is no dispute that the '068 patent was listed by the NDA holder, and that it was the "subject of the certification" Teva submitted in 2003 along with its ANDA for celecoxib. Submission of that certification established Teva as a first-filer with respect to the '068 patent. Further, FDA does not dispute that the May 13, 2008 Federal Circuit mandate was a final "decision of a court" holding the '068 patent invalid. FDA Decision at 1; J.A. 41. Thus, had this Court inquired of FDA (or Teva) on May 14, 2008, as to whether Teva's 180-day exclusivity tied to the '068 patent had been triggered and was then running, the answer would have been an unequivocal "yes." *See id*. But FDA claims that the statutory language somehow permits FDA to create a retroactive exception from the court decision trigger for court decisions on patents that are, years later, the subject of a reissue.

The starting point of any statutory analysis is the plain meaning of the provision itself. *See United States v. Lehman*, 225 F.3d at 426, 428 (4th Cir. 2000) ("A fundamental canon of statutory construction requires that 'unless otherwise

defined, words will be interpreted as taking their ordinary, contemporary, common meaning.'" (citing *Perrin v. United States*, 444 U.S. 37, 42 (1979)). As the District Court acknowledged, "the ordinary understanding of the words 'a' and 'the' is that they refer to singular items." J.A. 271-72. "At *Chevron* Step One, the Court 'must assume that the legislative purpose is expressed by the ordinary meaning of the words used.'" *Id*. (quoting *Apotex Inc. v. FDA*, 414 F. Supp. 61, 70 (D.D.C. 2006) (per curiam)). The District Court recognized that "it appears that Congress was referring only to original, and not all, patents when it drafted the court decision trigger clause," because the court decision trigger language refers to "*a* decision of a court [on] . . . *the* patent which is the subject of the certification." J.A. 272. Thus, even the District Court's decision acknowledges that a literal reading of the statutory language dictates that "the patent" refers only to the '068 patent, rather than to any combination of the '068 and '048 patents. It further follows that "*a* decision of a court" necessarily means a single court decision on the original patent, not multiple court decisions invalidating both an original patent and a reissue patent. Under the plain meaning of Section 505(j)(5)(B)(iv), when a final invalidity decision as to the '068 patent was rendered in 2008, Teva's exclusivity period began to run.

There is no statutory authority for FDA to resurrect a terminated exclusivity period. Indeed, neither FDA nor the District Court identified any statutory

provision that even arguably authorizes FDA to rewrite the statutory definition of a court decision trigger.

The meaning FDA seeks to attribute to the court decision trigger can only be achieved by inserting plural elements that are not in the statute. FDA asserts that "the patent" can be interpreted to refer to a "bundle of rights" composed of both the original and reissue patent. FDA Decision at 5; J.A. 45. By first-filing certifications to an original patent and timely filing a certification to a reissue patent, FDA contends, a generic drug manufacturer obtains a period of 180-day exclusivity tied to "the patent." FDA Decision at 9; J.A. 49. For that to be the case, however, the statutory phrase "the patent which is the subject of the certification" would have to be revised (essentially, rewritten) to allow for multiple final decisions of multiple courts invalidating both the original patent and the reissue patent. And the use by Congress of the singular term "patent" would have to be disregarded.[11] FDA has no authority to rewrite the unambiguous words of the statute.

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[11] Because the FDC Act defines "patent" as "a patent issued by the [PTO]" – which would include both original and reissue patents – original and reissue patents are separate patents for the purposes of the FDC Act. FDC Act § 505(m), 21 U.S.C. § 355(m) (2002).

This is not the first time FDA has given an erroneous interpretation to the plain language "a decision of a court." In *Torpharm, Inc. v. Shalala*, the court rejected FDA's argument that the there is any ambiguity in the provision, holding that "[t]he natural meaning of the statute's reference to 'the court' is 'the court that decides that the patent is invalid or not infringed.'" No. 97-1925, 997 WL 33472411, at *3 (D.D.C. Sept. 15, 1997). In *Mylan Pharms., Inc. v. Shalala*, the court held "that the FDA exceeded its authority in promulgating a regulation which is contrary to the plain meaning of the statut[ory] . . . phrase 'a decision of a court' . . . ." 81 F. Supp. 2d 30, 47 (D.D.C. 2000). In both *Torpharm* and *Mylan*, the District Court for the District of Columbia concluded that the natural meaning of the phrase "a decision of a court" refers to either a district or appellate court decision, regardless of whether the court's decision was subject to being appealed. *See Mylan*, 81 F. Supp. 2d at 47; *Torpharm*, 1997 WL 33472411, at *3. Similarly here, the natural meaning of "a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed" dictates that the provision must apply to "the patent which is the subject of the certification," regardless of whether that patent is later reissued.

Furthermore, FDA's creation of an exception from the court decision trigger for patents that are later the subject of a reissue is inconsistent with the rest of the statutory framework governing 180-day exclusivity, and produces absurd results.

The court decision trigger is meaningless without reference to the other statutory provisions governing the listing of patents in the Orange Book and ANDA applicant certifications to such patents. *See* FDC Act § 505(b)(1)(G), (j)(2)(A)(vii)(IV), 21 U.S.C. § 355 (b)(1)(G), (j)(2)(A)(vii)(VI). Together, these provisions create and define 180-day exclusivity. And each of these provisions has long been interpreted by FDA to apply to original patents and, separately, to reissue patents. Namely, an NDA holder must submit to FDA for listing in the Orange Book any original patent, and separately, *any reissue patent*, that covers its drug. *See* FDA Decision at 4; J.A. 44 ("the NDA applicant or holder is expected to submit the reissued patent for listing in the Orange Book . . . "). An ANDA applicant must then certify to each original patent and, separately, to *each reissue patent*. *See* FDA Decision at 5; J.A. 45 ("FDA believes it is appropriate to require ANDA applicants to amend their ANDAs to certify to a timely filed reissued patent . . ."). FDA's present assertion that the triggering provision, alone, applies to original and reissue patents as a "bundle" is the interpretive equivalent of deciding that "sugar," if it appears three times in a recipe as an ingredient, means "sugar" in two places, and "honey" in a third. Equally absurd is FDA's contradictory interpretations of the same word ("patent") in the Hatch-Waxman Amendments. FDA twice (with regard to listing and certifying) interprets it to mean that original and reissue patents are separate and distinct, and once (with

regard to the court decision trigger) to mean that an original and reissue patents are a "bundle of rights."

FDA's attempt to define "patent" differently in the context of the court decision trigger from how it defines that term elsewhere is at odds with the fundamental canon of statutory interpretation that "[a] term appearing in several places in a statutory text is generally read the same way each time it appears." *Ratzlaf v. United States*, 510 U.S. 135, 143 (1994); *see also Nat'l Credit Union Admin. v. First Nat'l Bank & Trust Co*., 522 U.S. 479, 501 (1998) ("similar language contained within the same section of a statute must be accorded consistent meaning"); *Tolbert v. Stevenson*, 635 F.3d 646 (4th Cir. 2011) (holding that repeated use of the term "action" within a single statutory section to encompass an entire case or suit confirmed that another use of "action" within that section had the same meaning). FDA's position that a "patent" constitutes a "bundle of rights" in only one instance of several within a single statutory section cannot withstand scrutiny.

FDA's interpretation also produces absurd results. Under the plain language of the court decision trigger, and applying common sense, when a first filer obtains a final court decision and thereby triggers the start of its 180-day exclusivity tied to the original patent, all of the competitors who were not first-filers would understand that the period of exclusivity will expire 180 days later, and act

accordingly. But, under FDA's tortured revision of the statute, the later filers cannot be at all certain that the exclusivity period expires as otherwise expected – nor commence the expensive and time-consuming preparations to market their products once the FDC Act permits generic competition – because at some point in the future a reissue patent may be issued that resuscitates the "zombie" exclusivity period. A statutory interpretation that produces absurd results cannot be condoned by this Court under any circumstances, and even more so when the plain language of the statute provides an approach that is rational. *See Green v. Bock Laundry Mach. Co.*, 490 U.S. 504, 527 (1989) (Scalia, J., concurring) (reasoning that the Court must avoid interpreting a statute to produce an absurd result where an alternative meaning is possible). The FDA Decision is contrary to the plain language of the statute and should be reversed.

2. The District Court's Decision on the Merits Was Based on an Erroneous Reading of the Statute.

The District Court failed to conduct the requisite analysis under *Chevron* Step One and exhaust traditional tools of statutory construction in determining whether Congress spoke clearly as to the precise question at issue here – namely, whether the Federal Circuit's 2008 mandate invalidating the '068 patent was a court decision trigger.

In determining that the statutory court decision trigger was ambiguous, the District Court's analysis erroneously conflated the questions of: (1) whether a

period of exclusivity tied to an original patent was triggered by "a decision of a court" on that patent, and thus expired 180 days later; and (2) whether reissue patents could give rise to a separate period of 180-day exclusivity. Echoing that error in the analysis, the District Court concluded that "ambiguity exists here with respect to the court decision trigger clause's treatment of exclusivity periods for reissued patents." J.A. 270. However, the issue with respect to the court decision trigger in this case is *not* its treatment of any exclusivity period tied to the '048 reissue patent, but its treatment of the exclusivity period tied to the original '068 patent, which was only much later the subject of a reissue.

Further, in reaching its conclusion, the District Court noted that "the 'court-decision trigger language [] does not necessarily define what causes the exclusivity entitlement to arise.'" *Id*. (citing *Apotex Inc. v. FDA*, 414 F. Supp. 2d at 71 (per curiam)). However, the occasional lack of clarity about whether certain conditions give rise to an "exclusivity entitlement" is immaterial to the plain statutory language defining the court decision trigger. Finally, as noted above, the District Court failed to act in accordance with its proper conclusion that the ordinary meaning of singular words used in the court decision trigger provision dictates that it was intended to apply to an original patent, likely because the District Court mistakenly focused on the entirely separate question of whether a separate period of 180-day exclusivity tied to a reissue patent exists. *Id*. at 21-22.

Notably, in similar instances in which FDA attempted to revise the text of the statutory 180-day exclusivity framework, reviewing courts reversed FDA at *Chevron* Step One, rather than deferring to agency language at odds with the statute, as the District Court did here. In *Granutec, Inc. v. Shalala*, for example, this Court determined that the same statutory provision at issue here *unambiguously* precluded FDA's regulation interpreting the statute to require that "the applicant submitting the first application has successfully defended against a suit for patent infringement." 139 F.3d 889, at *3 (4th Cir. 1998) (unpublished decision) (quoting 21 C.F.R. § 314.107(c)(1) (1997)). Employing traditional tools of statutory construction, the *Granutec* court reasoned that FDA's so-called "successful defense" interpretation "adds a requirement not contemplated in the statute, and . . . renders superfluous 21 U.S.C.A. § 355(j)(4)(B)(iv)(I), which allows the 180-day period to begin at the time FDA receives notice of marketing of the drug, regardless of the outcome of any infringement suit." *Id*. at *7. In the present case, FDA has added an *exception* not contemplated in the statute, and thereby rendered the court decision trigger at 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2002) entirely meaningless where there remains any possibility that the patent to which it applies could one day be reissued.

In *Inwood Labs., Inc. v. Young*, the U.S. District Court for the District of Columbia similarly determined that the statute was unambiguous on its face, and

FDA could not insert a provision – that did not exist – requiring patent litigation. 723 F. Supp. 1523, 1526 (D.D.C. 1989). The *Inwood* court reasoned that "[t]he two alternatives [for triggering 180-day exclusivity] are clear, and they establish a complete and workable statutory scheme . . . ." *Id.* Similarly, here, FDA's insertion of an extra-statutory exception undermines the proper functioning of the statutory scheme Congress devised.

Furthermore, if the District Court in this case were correct that the relevant statutory language ("the patent which is the subject of the certification") is ambiguous simply because it does not explicitly address every fact pattern covered by its language, virtually any language in any federal statute would be similarly ambiguous. There is no dispute that the '068 patent was the subject of the certification that Teva filed with FDA in November 2003. Nor is there any dispute that the May 2008 mandate of the Federal Circuit was a final court decision invalidating that patent – FDA admitted as much, twice, in the FDA Decision. *See* FDA Decision at 1, 1 n.1; J.A. 41.

To render the statute ambiguous, FDA must torture the language to mean that a "patent which is the subject of the certification" cannot include an original patent if that patent is later surrendered and replaced by a reissue patent, although the District Court also said that the interpretation advanced by Mylan is reasonable. J.A. 271. The District Court decided that this supposed ambiguity means that this

and other language about a "patent" that leads to a marketing exclusivity period cannot include a reissue patent. But that conclusion – even if it is accurate (and it is not, *see* Section III, *infra*) – does not compel, or even support, a finding that the court decision trigger does not include a court decision invalidating an original patent. The language, of course, does not exclude any particular type of patent from the definition of "the patent" invalidated, just as it does not exclude any kind of "final court decision" invalidating a patent.[12] The attempt to manufacture ambiguity about what "the patent" means is just as seriously flawed as FDA's previous attempts to reword the statutory provisions governing 180-day exclusivity, and closely resembles its attempt to exclude from the phrase "court decision" a decision dismissing an action for declaratory judgment.[13] Just as the courts rejected FDA's attempt to redefine "court decision" in that case, *Teva Pharms., USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999), this Court should dismiss FDA's attempt to redefine "the patent which is the subject of the certification" as not including the '068 patent. Accordingly, the FDA Decision and the District Court's decision should be reversed.

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[12] In fact, FDA treats other classes of patents, such as continuation and divisional patents, as falling under the "patent" definition.

[13] As noted above, "patent" is defined by the FDC Act to mean any patent issued by the PTO.

B. Even if the Statute Were Ambiguous, FDA's Interpretation of the Court Decision Trigger Is Not Reasonable.

Even if this Court does not find that the statutory court decision trigger compels reversal under *Chevron* Step One, the Court should set aside the FDA Decision under *Chevron* Step Two because it is not "based on a permissible construction of the statute," i.e., it is arbitrary and capricious. *Chevron*, 467 U.S. at 843-44. Agency action is arbitrary and capricious when it "entirely fail[s] to consider an important aspect of the problem, offer[s] an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of the United States v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

The FDA Decision constitutes an unexplained departure from FDA's long-standing and judicially recognized *ministerial* role with respect to patents by simultaneously interpreting patent law (which FDA is not charged with administering) and demonstrating that FDA lacks expertise to do so. FDA's "bundle of rights" approach to original and reissue patents is entirely unfounded in patent law, or in any prior FDA decision or action. Furthermore, FDA's "bundle of rights" interpretation produces an absurd situation wherein the statutory exclusivity period tied to an original patent is carried forward by virtue of a reissue patent, but the statutory triggering and expiration of that exclusivity is *not* carried

forward. Finally, FDA's approach is unreasonable from a policy perspective, because it sows confusion and is demonstrably not, as FDA claims, a vehicle for consistency and predictability.

FDA has long asserted that its role regarding patents under the Hatch-Waxman Amendments is purely ministerial. *See aaiPharma Inc. v. Thompson*, 296 F.3d 227, 241 (4th Cir. 2002); *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 125 (D.C. Cir. 2006), *abrogated by Teva Pharms. USA*, 595 F.3d 1303; *Am. Bioscience, Inc.*, 269 F.3d at 1084; *Mylan Pharms., Inc. v. Thompson*, 139 F. Supp. 2d 1, 10-11 (D.D.C. 2001), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001). FDA has no expertise in patent law, and its considerations of patent law are not entitled to any judicial deference. *See Bd. of Governors of Univ. of N. Carolina v. U.S. Dep't of Labor*, 917 F.2d 812, 816 (4th Cir. 1990) ("In those instances where an agency has ruled on a question of law outside of its area of expertise, we no longer defer to the rulings of the agency, but instead conduct the more searching inquiry of de novo review."); *Shanty Town Assocs. Ltd. P'ship v. E.P.A.*, 843 F.2d 782, 791 n.12 (4th Cir. 1988). Yet, the FDA Decision, which promulgated a "bundle of rights" approach to original and reissue patents, required FDA to delve into the relative complexities of the patent statute and regulations governing those types of patents. *See* FDA Decision at 3-4; J.A. 43-44.

FDA's foray into patent law demonstrates that FDA should be required to continue to follow a ministerial approach. The only case FDA cited in the FDA Decision and before the District Court to justify its "bundle of rights" theory, *Vaupel Textilmaschinen KG v. Meccanica Euro Italia S.P.A.*, 944 F.2d 870, 875 (Fed. Cir. 1991), is inapposite, and FDA's reliance on *Vaupel* evinces a fundamental misunderstanding of the "bundle of rights" concept under patent law. *Vaupel*, like other cases discussing a bundle of patent rights, relates specifically to the "bundle of rights" associated with a single patent, which can be divided and assigned to licensees. In other words, rather than bundling two patents together to create the "bundle of rights" invented by FDA, patent cases discussing the "bundle of rights" recognize that a single patent can bestow this bundle, even if the patent is a reissue patent. *See Zoltek Corp. v. United States*, 58 Fed. Cl. 688, 698 (Fed. Cl. 2003) (applying the "bundle of rights" approach to a reissue patent, without reference to the original patent); *see also MobileMedia Ideas, LLC v. Apple, Inc.*, 885 F. Supp. 2d 700, 707 (D. Del. 2012) (in a case involving sixteen patents, including at least one reissue patent, the court reasoned with respect to those patents that "[a] patent is a bundle of rights which may be divided and assigned or retained in whole or in part" (internal quotations omitted)). By the logic of these "bundle of rights" patent cases, the '048 reissue patent would be a completely

separate "bundle of rights" disconnected from the "bundle of rights" that comprised the original '068 patent before its surrender.

Moreover, over a hundred and fifty years of patent case law dictates that a reissue patent is separate and distinct from the original patent, not a "bundle of rights" with the original. *See, e.g.*, *Peck v. Collins*, 103 U.S. 660, 664 (1880) ("[I]f a reissue is granted, the patentee has no rights except such as grow out of the reissued patent. He has none under the original. That is extinguished."); *Russell v. Dodge*, 93 U.S. 460, 463 (1876) (characterizing a reissue patent as a "new patent"); *Moffitt v. Garr*, 66 U.S. 273, 279 (1861) ("[T]he act of surrender extinguishes the right of the action so far as the old patent is concerned . . . . The only right saved is under a reissue, and in virtue of the new patent . . . [B]ut the only rights which survive the surrender [of the original patent], survive alone by virtue of the new patent."); *O'Reilly v. Morse*, 56 U.S. 62, 112 (1853) (describing reissue as "[t]he right to surrender the old patent, and receive another in its place"); *Grant v. Raymond*, 31 U.S. 218, 224 (1832) (referring to a reissue patent as a "new patent").[14]

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[14] *See also Senju Pharm. Co., Ltd. v. Apotex Inc.*, 746 F.3d 1344 (Fed. Cir. 2014) (reaffirming *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335 (Fed. Cir. 2012)); *Aspex Eyewear, Inc.*, 672 F.3d at 1341-42 (describing reissue as "the issuance of a new patent."); *Seattle Box Co., Inc. v. Indus. Crating & Packing,*

Nor can FDA's "bundle of rights" approach with regard to the court decision trigger be traced to the precedents FDA cites in the FDA Decision: the FDA letters on Mircette, Ultracet and Adderall. *See* FDA Decision at 7-8; J.A. 47-48. None of these prior letter decisions were put before a court to test whether it was consistent with the statute. Further, none of FDA's cited examples involved an exclusivity period tied to an original patent that would have expired – based on operation of the court decision trigger – years before the reissue patent issued. FDA acknowledges as much in the FDA Decision, noting that in the three examples it cites exclusivity was deemed to be triggered by either a court decision on the *reissue* patent, or by commercial marketing. FDA Decision at 9; J.A. 49. Application of the court decision trigger to an original patent was not at issue in those instances.

Furthermore, in the case of fluoxetine, a drug that FDA does not cite in the FDA Decision but that Mylan raised before the District Court , there was a final

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Inc., 731 F.2d 818, 829 (Fed. Cir. 1984) ("When a reissue patent issues, a new patent with presumably valid claims exists."); *Freeman v. Altvater*, 138 F.2d 854, 857 (8th Cir. 1943) ("Reissue is the act of the commissioner in granting a new patent."); *Mobile Shelter Sys. USA, Inc. v. Grate Pallet Solutions, LLC*, No. 10-978, 2011 WL 7030963, at *2 (M.D. Fla. Nov. 10, 2011) ("[T]he law is abundantly clear that an original patent is void and unenforceable after it is surrendered in a reissue proceeding."); *Nellcor Puritan Bennett LLC v. CAS Med. Sys., Inc*., No. 11-cv-15697, 2012 WL 3525636 (E.D. Mich. Aug. 14, 2012) (recognizing a reissue patent as a new and distinct patent); *House v. Young*, 12 F. Cas. 598 (N.D. Ohio 1867) (No. 6738) (referring to a reissue patent as a "new patent").

court decision of non-infringement with respect to both an original and a reissue patent, as well as a third patent. FDA's approval letter to a subsequent ANDA applicant that was blocked by the first-filer's exclusivity identifies each of the three patents tied to that exclusivity, but nowhere suggests that the three patents (or two of the three patents, the original and the reissue) are "bundled" together to create exclusivity. Indeed, FDA did not distinguish the original and reissue patent from the third patent at all. *See* Fluoxetine Delayed-release Capsules, 90 mg (Once-Weekly), Approval Letter, ANDA No. 078572 (Mar. 22, 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/078572s000ltr.pdf.

Similarly, even if FDA's "bundle of rights" approach were a linguistically feasible interpretation of the statutory language, which it is not, the interpretation is not a permissible or reasonable one because it produces the absurd result that a 180-day exclusivity period would carry forward from an original to a reissue patent, while the triggering and expiration of that same period do *not* carry forward. By its interpretation, FDA is arbitrarily cherry-picking when original patents and reissue patents create a "bundle of rights," and when they do not.

Finally, FDA's interpretation of the statute unnecessarily introduces uncertainty into the framework governing 180-day exclusivity. If an expired marketing exclusivity period can be resuscitated when a patent is reissued – even 58 months (or more) after the exclusivity period expired – there can be no

predictability for ANDA applicants that they will be able to market once they receive final approval, because a reissue patent could be sought and granted at any time.

III. FDA'S DENIAL OF SHARED EXCLUSIVITY TO FIRST-FILERS TO THE '048 PATENT IS INCONSISTENT WITH THE STATUTE, ARBITRARY, AND CAPRICIOUS.

FDA's denial of shared 180-day exclusivity to the first-filers to certify to the '048 patent is inconsistent with the FDC Act, arbitrary, and capricious. The statute dictates that Mylan, Watson, and Teva be granted shared 180-day exclusivity under the framework of the Hatch-Waxman Amendments.

Under *Chevron* Step One, the language of the FDC Act is clear: exclusivity can be associated with "any" patent. Specifically, as summarized above, the Hatch-Waxman Amendments set out a series of conditions that, when met, create 180-day exclusivity. These provisions dictate first that an NDA sponsor submit with its application "the patent number and the expiration date of *any patent* which claims the drug for which the applicant submitted the [NDA] or which claims a method of using such drug . . . ." FDC Act § 505(b)(1)(G); 21 U.S.C. § 355(b)(1)(G) (emphasis added). FDA publishes the patent information in the Orange Book. FDC Act § 505(b)(1), (c)(2), 21 U.S.C. § 355(b)(1), (c)(2). The FDC Act then requires each ANDA applicant to submit a certification "with respect to *each patent* which claims the listed drug . . . or which claims a use for

such listed drug . . . ." FDC Act § 505(j)(2)(A)(vii), 21 U.S.C. § 355(j)(2)(A)(vii) (emphasis added). FDA has consistently treated these requirements as applying to both original and reissue patents, as discussed in the FDA Decision. FDA Decision at 4-5; J.A. 44-45. Because there is no distinction in the statute between original patents and reissue patents – and indeed the FDA has treated the statute as applying to both – an exclusivity period for each patent must likewise occur under the plain language of the statute. As discussed further below, the fact that FDA followed a patent-by-patent approach to exclusivity periods for a drug with an ANDA that predates MMA (like celecoxib) supports the conclusion that separate exclusivity periods should be awarded for original and reissue patents.

FDA's denial of a shared period of exclusivity is also invalid under *Chevron* Step Two. FDA's position, adopted by the District Court, was that Teva's revived period of sole 180-day exclusivity tied to the '068 patent and '048 patent was a "bundle" that somehow precluded shared exclusivity among the first-filers to the '048 patent. As such, FDA denied first-filers to the '048 patent their right to a 180-day exclusivity period tied to the reissue patent (except Teva, which gains an undeserved period of sole exclusivity in place of the exclusivity it should have shared with Mylan, Watson, and perhaps others).

FDA's denial of shared exclusivity tied to the '048 patent conflicts with the statutory framework established by the pre-MMA Hatch-Waxman Amendments,

and it arbitrarily treats first-filers to the '048 patent differently from first-filers to an original patent.

First, there can be no question that, in the pre-MMA regime for exclusivity periods, FDA embraced a patent-by-patent approach to exclusivity. This approach permitted multiple periods of exclusivity to be awarded for generic versions of the same drug, if different companies were first-filers to different patents covering that drug. *See Apotex Inc. v. FDA*, 414 F. Supp. 2d 61 (D.D.C. 2006), *aff'd*, 226 F. App'x 4 (D.C. Cir. 2007). *See also Watson Labs., Inc. v. Sebelius*, No. 12-1344, 2012 WL 6968224, at *3 n.2 (D.D.C. Oct. 22, 2012) ("FDA indicates that prior to the 2003 amendments, it granted exclusivity on a patent-by-patent basis. This meant that a period of exclusivity could potentially arise for each patent claimed by a drug." (citation omitted)). In fact, FDA continues to acknowledge that the patent-by-patent framework applies in pre-MMA cases. FDA Decision at 3; J.A. 43 ("[R]egulations governing pre-MMA 180-day exclusivity should be interpreted to award such exclusivity on a patent-by-patent basis. That is, eligibility for 180-day exclusivity would be based on which company submitted the first paragraph IV certification challenging each listed patent." (footnote omitted)). FDA deviated from its patent-by-patent framework when it refused to grant shared exclusivity to the first-filers to the '048 patent.

Agencies like FDA are required to treat like situations alike. *See Burlington N. and Santa Fe Ry. Co. v. Surface Trans. Bd.*, 403 F.3d 771, 777 (D.C. Cir. 2005) ("Where an agency applies different standards to similarly situated entities and fails to support this disparate treatment with a reasoned explanation and substantial evidence in the record, its action is arbitrary and capricious and cannot be upheld." (citations omitted)) .[15] Yet FDA did exactly what courts have proscribed: according disparate treatment without reasoned explanation. The FDA Decision treated two functionally indistinguishable categories of ANDA applicants – those who submit Paragraph IV certifications to a reissue patent and those who submit Paragraph IV certifications to an original patent – differently, without a justifiable explanation for doing so. As such, the FDA Decision was arbitrary and capricious and must be reversed.

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[15] *See also Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) ("Government is at its most arbitrary when it treats similarly situated people differently" (quoting *Etelson v. Office of Pers. Mgmt.*, 684 F.2d 918, 926 (D.C. Cir. 1982))); *United States v. Diapulse Corp. of Am.*, 748 F.2d 56, 62 (2d Cir. 1984) (holding that FDA must act "evenhandedly" and may "not 'grant to one person the right to do that which it denies to another similarly situated'" (quoting *Marco Sales Co. v. FTC*, 453 F.2d 1, 7 (2d Cir. 1971))); *Int'l Rehabilitative Sci., Inc. v. Kessler*, No. SA-93-CA-0242, Medical Devices Reporter (CCH) ¶ 15,181 (W.D. Tex. June 29, 1993) (finding that FDA's "divergent treatment" of two muscle stimulator devices was "glaring evidence of arbitrary action.").

The Hatch-Waxman Amendments create a balanced incentive structure intended to both protect the rights of patent holders and encourage the introduction of lower-cost generic products into the U.S. market. Slip. Op. at 5-7; J.A. 255-57. Courts have rejected actions taken by FDA that would interfere with this incentive structure established by Congress. *See Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006) (finding that an FDA decision that would have deprived an ANDA applicant of 180-day exclusivity after that applicant fulfilled the statutory requirements was "inconsistent with the text and structure of the Act and, because it diminishes the incentive the Congress gave manufacturers of generic drugs, is inconsistent with the purpose of the Act."); *Ranbaxy Labs., Ltd. v. Leavitt*, 459 F. Supp. 2d 1 (D.D.C. 2006).

Yet, the FDA Decision in this case similarly diminishes the statutory incentive structure by depriving Mylan and Watson of the shared statutory exclusivity period to which they are entitled after having borne the risks and costs associated with fulfilling the statutory requirements for exclusivity.

If an ANDA applicant chooses to submit a Paragraph IV certification to a listed patent, thereby challenging that patent by declaring it to be invalid or not infringed, it exposes itself to costly and potentially lengthy patent litigation initiated by the patent holder. The statutory incentive for taking this costly step,

and helping to clear the way for the earlier marketing of generic products, is that a first-filed Paragraph IV certification creates the basis for 180-day exclusivity.

FDA agrees that each of the statutory provisions mentioned above, regarding the listing of patents and certification to those patents, applies equally to original and reissue patents. And indeed, it is clear from the facts of this case that the risk and costs of patent litigation borne by ANDA applicants who certify to a reissue patent are equal to those borne by ANDA applicants who certify to an original patent. *See G.D. Searle LLC v. Lupin Pharms., Inc.*, No. 2:13-cv-00121 (E.D. Va. Mar. 14, 2014) (patent infringement litigation brought by G.D. Searle and Pfizer against Mylan, Watson, Lupin, Teva, and Apotex based on those companies' certifications to the '048 patent); J.A. 53. FDA offers no rationale for the disconnect between that undisputed fact and its unfounded determination that "FDA does not consider a reissued patent to be a new and distinct patent for purposes of 180-day exclusivity." FDA Decision at 5; J.A. 45. While FDA asserts that its purpose is to "consistently and predictably implement the FD&C Act," *id.*, and states conclusorily that its action is "consistent with the objectives of the Hatch-Waxman Amendments," FDA Decision at 9; J.A. 49, FDA fails to address or even acknowledge the damage its approach works on the basic statutory framework of incentives that Act creates. This is the essence of arbitrary and capricious decision making. *See Motor Vehicle Mfr's. Ass'n. of the United States,*

463 U.S. at 43, 52 (agency decision-making is arbitrary and capricious where the agency "entirely failed to consider an important aspect of the problem," or fails to "offer a 'rational connection between the facts found and the choice made.'"); *see also Ohio River Valley Envtl. Coal., Inc. v. Kempthorne*, 473 F.3d 94, 103 (4th Cir. 2006) (holding an EPA determination to be arbitrary and capricious where the Agency failed to explain why the promulgated change "with the potential to alter the . . . process in a way that may make it less environmentally protective is nevertheless consistent with the [Surface Mining Control and Reclamation Act].").

CONCLUSION

This Court should reverse the District Court's decision upholding FDA's determination that Teva's marketing exclusivity period tied to the '068 patent did not expire in November 2008, and instruct the District Court to enter a Declaratory Judgment to that effect. Mylan and Watson also urge this Court to instruct the District Court to enter a Declaratory Judgment that FDA should award a separate, shared exclusivity period to eligible first-filers to the '048 patent.

Respectfully submitted,

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CERTIFICATION OF COMPLIANCE
UNDER FED. R. APP. P. 32(a)(7)

Pursuant to Fed. R. App. P. 32(a)(7)(C)(i), I hereby certify that the foregoing Brief for Plaintiffs-Appellants Mylan Pharmaceuticals Inc. and Watson Laboratories, Inc. complies with Fed. R. App. P.32(a)(7)(B)(i) because it contains 10,878 words, excluding the Corporate Disclosure Statement, Table of Contents, Table of Authorities, Addendum containing statutes, Certificate of Service, and this Certificate of Compliance. I also certify that this Brief complies with the typeface and style requirements of Fed. R. App. P. 32(a)(5) and (6), because it has been prepared using Microsoft Word with a proportionally spaced 14-point Times New Roman font.

/s/ Douglas B. Farquhar
(signature)

July 3, 2014
(date)

CERTIFICATE OF SERVICE

I certify that on July 3, 2014, the foregoing document was served on all parties or their counsel of record through the CM/ECF system.

/s/ Douglas B. Farquhar
(signature)

July 3, 2014
(date)

NO. 14-1522 (L)

United States Court of Appeals

for the

Fourth Circuit

MYLAN PHARMACEUTICALS INC.,
WATSON LABORATORIES, INC.,
and
LUPIN PHARMACEUTICALS, INC.

Plaintiffs-Appellants

– v. –

U.S. FOOD AND DRUG ADMINISTRATION
and
TEVA PHARMACEUTICALS USA, INC.

Defendants-Appellees

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR
THE NORTHERN DISTRICT OF WEST VIRGINIA AT CLARKSBURG

ADDENDUM

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(d) Regulations

(1) In general

The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A) of this section, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

(2) Limiting compounding

The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) of this section for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

(e) Application

This section shall not apply to—

(1) compounded positron emission tomography drugs as defined in section 321(ii) of this title; or

(2) radiopharmaceuticals.

(f) "Compounding" defined

As used in this section, the term ''compounding'' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

(June 25, 1938, ch. 675, § 503A, as added Pub. L. 105–115, title I, § 127(a), Nov. 21, 1997, 111 Stat. 2328.)

EFFECTIVE DATE

Section 127(b) of Pub. L. 105–115 provided that: ''Section 503A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 353a], added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act [Nov. 21, 1997].''

§ 354. Veterinary feed directive drugs

(a) Lawful veterinary feed directive requirement

(1) A drug intended for use in or on animal feed which is limited by an approved application filed pursuant to section 360b(b) of this title to use under the professional supervision of a licensed veterinarian is a veterinary feed directive drug. Any animal feed bearing or containing a veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice. When labeled, distributed, held, and used in accordance with this section, a veterinary feed directive drug and any animal feed bearing or containing a veterinary feed directive drug shall be exempt from section 352(f) of this title.

(2) A veterinary feed directive is lawful if it—

(A) contains such information as the Secretary may by general regulation or by order require; and

(B) is in compliance with the conditions and indications for use of the drug set forth in the notice published pursuant to section 360b(i) of this title.

(3)(A) Any persons involved in the distribution or use of animal feed bearing or containing a veterinary feed directive drug and the licensed veterinarian issuing the veterinary feed directive shall maintain a copy of the veterinary feed directive applicable to each such feed, except in the case of a person distributing such feed to another person for further distribution. Such person distributing the feed shall maintain a written acknowledgment from the person to whom the feed is shipped stating that that person shall not ship or move such feed to an animal production facility without a veterinary feed directive or ship such feed to another person for further distribution unless that person has provided the same written acknowledgment to its immediate supplier.

(B) Every person required under subparagraph (A) 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.

(C) Any person who distributes animal feed bearing or containing a veterinary feed directive drug shall upon first engaging in such distribution notify the Secretary of that person's name and place of business. The failure to provide such notification shall be deemed to be an act which results in the drug being misbranded.

(b) Labeling and advertising

A veterinary feed directive drug and any feed bearing or containing a veterinary feed directive drug shall be deemed to be misbranded if their labeling fails to bear such cautionary statement and such other information as the Secretary may by general regulation or by order prescribe, or their advertising fails to conform to the conditions and indications for use published pursuant to section 360b(i) of this title or fails to contain the general cautionary statement prescribed by the Secretary.

(c) Nonprescription status

Neither a drug subject to this section, nor animal feed bearing or containing such a drug, shall be deemed to be a prescription article under any Federal or State law.

(June 25, 1938, ch. 675, § 504, as added Pub. L. 104–250, § 5(b), Oct. 9, 1996, 110 Stat. 3155.)

PRIOR PROVISIONS

A prior section 354, act June 25, 1938, ch. 675, § 504, 52 Stat. 1052, which directed Secretary to promulgate reg-

ulations for listing of coal-tar colors, was repealed effective July 12, 1960, subject to provisions of section 203 of Pub. L. 86–618, by Pub. L. 86–618, title I, § 103(a)(2), title II, § 202, July 12, 1960, 74 Stat. 398, 404.

SECTION REFERRED TO IN OTHER SECTIONS

This section is referred to in sections 331, 360b of this title.

§ 355. New drugs

(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; and (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).

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

(B) The notice referred to in subparagraph (A) shall state that an application 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. 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.

(C) If an application is amended to include a certification described in paragraph (2)(A)(iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(4)(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 under the following:

(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 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 (3)(B) is received. 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 paragraph (3)(B) 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 may 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 may be made effective on such date as the court orders under section 271(e)(4)(A) of title 35, 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 effective 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 (3)(B) is received, no action may be brought under section 2201 of title 28 for a declaratory judgment with respect to the patent. Any action brought under such 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.

(D)(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 bioavailabilty[1] 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

[1] So in original. Probably should be ''bioavailability''.

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 main-

taining 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 therefor, 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)(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) of this section 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)(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 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, 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 effective 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, 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) 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) ap-

plication 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) 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.

(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 traveltime, 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.

(June 25, 1938, ch. 675, § 505, 52 Stat. 1052; Pub. L. 86–507, § 1(18), June 11, 1960, 74 Stat. 201; Pub. L. 87–781, title I, §§ 102(b)–(d), 103(a), (b), 104(a)–(d)(2), Oct. 10, 1962, 76 Stat. 781–783, 784, 785; Pub. L. 92–387, § 4(d), Aug. 16, 1972, 86 Stat. 562; Pub. L. 98–417, title I, §§ 101, 102(a)–(b)(5), 103, 104, Sept. 24, 1984, 98 Stat. 1585, 1592, 1593, 1597; Pub. L. 102–282, § 5, May 13, 1992, 106 Stat. 161; Pub. L. 103–80, § 3(n), Aug. 13, 1993, 107 Stat. 777; Pub. L. 105–115, title I, §§ 115, 117, 119, 120, 124(a), Nov. 21, 1997, 111 Stat. 2313, 2315, 2316, 2318, 2324; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(b)(11)], Nov. 29, 1999, 113 Stat. 1536, 1501A–584; Pub. L. 107–109, § 15(c)(1), Jan. 4, 2002, 115 Stat. 1420.)

REFERENCES IN TEXT

The General Schedule, referred to in subsec. (n)(6), is set out under section 5332 of Title 5, Government Organization and Employees.

AMENDMENTS

2002—Subsec. (i)(1)(D). Pub. L. 107–109 added subpar. (D).

1999—Subsec. (m). Pub. L. 106–113 substituted ''United States Patent and Trademark Office'' for ''Patent and Trademark Office of the Department of Commerce''.

1997—Subsec. (b)(1). Pub. L. 105–115, § 115(b), inserted at end ''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).''

Subsec. (b)(4). Pub. L. 105–115, § 119(a), added par. (4).

Subsec. (c)(4). Pub. L. 105–115, § 124(a), added par. (4).

Subsec. (d). Pub. L. 105–115, § 115(a), inserted at end ''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.''

Subsec. (i). Pub. L. 105–115, § 117, inserted ''(1)'' after ''(i)'', redesignated former pars. (1) to (3) as subpars. (A) to (C), respectively, of par. (1), added pars. (2) to (4), and struck out closing provisions which read as follows: ''Such regulations 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 they deem it not feasible or, in their professional judgment, 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.''

Subsec. (j)(2)(A)(i). Pub. L. 105–115, § 119(b)(2)(A), substituted ''paragraph (7)'' for ''paragraph (6)''.

Subsec. (j)(3). Pub. L. 105–115, § 119(b)(1)(B), added par. (3). Former par. (3) redesignated (4).

Subsec. (j)(4). Pub. L. 105–115, § 119(b)(1)(A), (2)(B), redesignated par. (3) as (4) and in introductory provisions substituted ''paragraph (5)'' for ''paragraph (4)''. Former par. (4) redesignated (5).

Subsec. (j)(4)(I). Pub. L. 105–115, § 119(b)(2)(C), substituted ''paragraph (6)'' for ''paragraph (5)''.

Subsec. (j)(5), (6). Pub. L. 105–115, § 119(b)(1)(A), redesignated pars. (4) and (5) as (5) and (6), respectively. Former par. (6) redesignated (7).

Subsec. (j)(7). Pub. L. 105–115, § 119(b)(1)(A), (2)(D), redesignated par. (6) as (7) and in subpar. (C) substituted ''paragraph (6)'' for ''paragraph (5)'' in two places. Former par. (7) redesignated (8).

Subsec. (j)(8), (9). Pub. L. 105–115, § 119(b)(1)(A), redesignated pars. (7) and (8) as (8) and (9), respectively.

Subsec. (n). Pub. L. 105–115, § 120, added subsec. (n).

1993—Subsec. (j)(6)(A)(ii). Pub. L. 103–80, § 3(n)(1)(A), substituted ''Secretary'' for ''Secretry''.

Subsec. (j)(6)(A)(iii). Pub. L. 103–80, § 3(n)(1)(B), inserted comma after ''published by the Secretary''.

Subsec. (k)(1). Pub. L. 103–80, § 3(n)(2), substituted ''section. Regulations'' for ''section: *Provided, however*, That regulations''.

1992—Subsec. (j)(8). Pub. L. 102–282 added par. (8).

1984—Subsec. (a). Pub. L. 98–417, § 102(b)(1), inserted ''or (j)'' after ''subsection (b)''.

Subsec. (b). Pub. L. 98–417, §§ 102(a)(1), 103(a), designated existing provisions of subsec. (b) as par. (1) thereof and redesignated existing cls. (1) through (6) of such par. (1) as cls. (A) through (F) thereof, respectively, inserted requirement that the applicant 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 by asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, that the applicant amend the application to include such information 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, and that upon approval of the application, the Secretary publish the information submitted, and added pars. (2) and (3).

Subsec. (c). Pub. L. 98–417, §§ 102(a)(2), (b)(2), 103(b), designated existing provisions of subsec. (c) as par. (1)

thereof and in par. (1) as so designated substituted ''subsection (b) of this section'' for ''this subsection'' and redesignated former pars. (1) and (2) as subpars. (A) and (B), respectively, and added pars. (2) and (3).

Subsec. (d)(6), (7). Pub. L. 98–417, §102(a)(3)(A), added cl. (6) relating to the failure of the application to contain the patent information prescribed by subsec. (b) of this section, and redesignated former cl. (6) as (7).

Subsec. (e). Pub. L. 98–417, §102(a)(3)(B), in first sentence, added a new cl. (4) relating to the failure to file the patent information prescribed by subsec. (c) of this section within 30 days after the receipt of written notice from the Secretary specifying the failure to file such information, and redesignated former cl. (4) as (5).

Pub. L. 98–417, §102(b)(3), (4), in second sentence, inserted in provisions preceding cl. (1) ''submitted under subsection (b) or (j) of this section'' and in cl. (1) substituted ''under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title'' for ''under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title''.

Subsecs. (j), (k). Pub. L. 98–417, §101, added subsec. (j) and redesignated former subsec. (j) as (k).

Subsec. (k)(1). Pub. L. 98–417, §102(b)(5), substituted ''under subsection (b) or (j) of this section'' for ''pursuant to this section''.

Subsecs. (*l*), (m). Pub. L. 98–417, §104, added subsecs. (*l*) and (m).

1972—Subsec. (e). Pub. L. 92–387 inserted ''or to comply with the notice requirements of section 360(j)(2) of this title'' in cl. (1) of second sentence relating to the maintenance of records.

1962—Subsec. (a). Pub. L. 87–781, §104(a), inserted ''an approval of'' before ''an application''.

Subsec. (b). Pub. L. 87–781, §102(b), inserted ''and whether such drug is effective in use'' after ''is safe for use''.

Subsec. (c). Pub. L. 87–781, §104(b), substituted provisions requiring the Secretary, within 180 days after filing an application, or such additional period as the Secretary and the applicant agree upon, to either approve the application, if meeting the requirements of subsec. (d) of this section, or give notice of opportunity for hearing on question of whether such application is approvable, and providing that if applicant requests hearing in writing within 30 days, the hearing shall begin within 90 days after expiration of said 30 days, unless the Secretary and applicant agree otherwise, that such hearing shall be expedited, and that the Secretary's order shall be issued within 90 days after date for filing final briefs, for provisions which had an application become effective on the sixtieth day after filing thereof unless prior thereto the Secretary postponed the date by written notice to such time, but not more than 180 days after filing, as the Secretary deemed necessary to study and investigate the application.

Subsec. (d). Pub. L. 87–781, §102(c), inserted references to subsec. (c), added cls. (5) and (6), provided that if after notice and opportunity for hearing, the Secretary finds that cls. (1) to (6) do not apply, he shall approve the application, and defined ''substantial evidence'' as used in this subsection and subsec. (e) of this section.

Subsec. (e). Pub. L. 87–781, §102(d), amended subsec. (e) generally, and among other changes, directed the Secretary to withdraw approval of an application if by tests, other scientific data or experience, or new evidence of clinical experience not contained in the application or available at the time of its approval, the drug is shown to be unsafe, or on the basis of new information, there is shown a lack of substantial evidence that the drug has the effect it is represented to have, and provided that if the Secretary, or acting Secretary, finds there is an imminent hazard to the public health, he may suspend approval immediately, notify the applicant, and give him opportunity for an expedited hearing, that the Secretary may withdraw approval if the applicant fails to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain records and make reports, or has refused access to, or copying or verification of such records, or if the Secretary finds on new evidence that the methods, facilities and controls in the manufacturing, processing, and packing are inadequate to assure and preserve the drugs' identity, strength, quality and purity, and were not made adequate within a reasonable time after receipt of written notice thereof, or finds on new evidence, that the labeling is false or misleading and was not corrected within a reasonable time after receipt of written notice thereof.

Subsec. (f). Pub. L. 87–781, §104(c), substituted provisions requiring the Secretary to revoke any previous order under subsecs. (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and to approve such application or reinstate such approval, for provisions which required him to revoke an order refusing effectiveness to an application.

Subsec. (h). Pub. L. 87–781, §104(d)(1), (2), inserted ''as provided in section 2112 of title 28'', and ''except that until the filing of the record the Secretary may modify or set aside his order'', substituted ''or withdrawing approval of an application under this section'' for ''to permit the application to become effective, or suspending the effectiveness of the application'', ''United States court of appeals for the circuit'' for ''district court of the United States within any district'', ''Court of Appeals for the District of Columbia Circuit'' for ''District Court for the District of Columbia'', ''transmitted by the clerk of the court to'' for ''served upon'', and ''by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28'' for ''as provided in sections 225, 346, and 347 of title 28, as amended, 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'', and eliminated ''upon'' before ''any officer designated'', ''a transcript of'' before ''the record'' and ''and decree'' before ''of the court affirming''.

Subsec. (i). Pub. L. 87–781, §103(b), inserted ''the foregoing subsections of'' after ''operation of'', and ''and effectiveness'' after ''safety'', and provided that the regulations may condition exemptions upon the submission of reports of preclinical tests to justify the proposed clinical testing, upon the obtaining by the manufacturer or sponsor of the investigation of a new drug of a signed agreement from each of the investigators that patients to whom the drug is administered will be under his supervision or under investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings, or upon the establishment and maintenance of records and reports of data obtained by the investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug, and provided that the regulations shall condition an exemption upon the manufacturer or sponsor of the investigation requiring that experts using such drugs certify that they will inform humans to whom such drugs or any controls connected therewith are administered, or their representatives, and will obtain the consent of such people where feasible and not contrary to the best interests of such people, and that reports on the investigational use of drugs are not required to be submitted directly to the Secretary.

Subsec. (j). Pub. L. 87–781, §103(a), added subsec. (j).

1960—Subsec. (g). Pub. L. 86–507 inserted ''or by certified mail'' after ''registered mail''.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, §4731] of Pub. L. 106–113, set out as a note under section 1 of Title 35, Patents.

EFFECTIVE DATE OF 1997 AMENDMENT

Amendment by Pub. L. 105–115 effective 90 days after Nov. 21, 1997, except as otherwise provided, see section 501 of Pub. L. 105–115, set out as a note under section 321 of this title.

EFFECTIVE DATE OF 1984 AMENDMENT

Section 105 of Pub. L. 98–417 provided that:

''(a) The Secretary of Health and Human Services shall promulgate, in accordance with the notice and comment requirements of section 553 of title 5, United States Code, such regulations as may be necessary for the administration of section 505 of the Federal Food, Drug, and Cosmetic Act [this section], as amended by sections 101, 102, and 103 of this Act, within one year of the date of enactment of this Act [Sept. 24, 1984].

''(b) During the period beginning sixty days after the date of the enactment of this Act [Sept. 24, 1984], and ending on the date regulations promulgated under subsection (a) take effect, abbreviated new drug applications may be submitted in accordance with the provisions of section 314.2 of title 21 of the Code of Federal Regulations and shall be considered as suitable for any drug which has been approved for safety and effectiveness under section 505(c) of the Federal Food, Drug, and Cosmetic Act [subsec. (c) of this section] before the date of the enactment of this Act. If any such provision is inconsistent with the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act, the Secretary shall consider the application under the applicable requirements of such section. The Secretary of Health and Human Services may not approve such an abbreviated new drug application which is filed for a drug which is described in sections 505(c)(3)(D) and 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act, except in accordance with such section.''

EFFECTIVE DATE OF 1972 AMENDMENT

Amendment by Pub. L. 92–387 effective on first day of sixth month beginning after Aug. 16, 1972, see section 5 of Pub. L. 92–387, set out as a note under section 360 of this title.

EFFECTIVE DATE OF 1962 AMENDMENT

Amendment by Pub. L. 87–781 effective on first day of seventh calendar month following October 1962, see section 107 of Pub. L. 87–781, set out as a note under section 321 of this title.

CONSTRUCTION OF AMENDMENTS BY PUB. L. 102–282

Amendment by Pub. L. 102–282 not to preclude any other civil, criminal, or administrative remedy provided under Federal or State law, including any private right of action against any person for the same action subject to any action or civil penalty under an amendment made by Pub. L. 102–282, see section 7 of Pub. L. 102–282, set out as a note under section 335a of this title.

TRANSFER OF FUNCTIONS

For transfer of functions of Federal Security Administrator to Secretary of Health, Education, and Welfare [now Health and Human Services], and of Food and Drug Administration in the Department of Agriculture to Federal Security Agency, see note set out under section 41 of this title.

REPORT ON PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER

Pub. L. 107–109, § 15(d), Jan. 4, 2002, 115 Stat. 1421, provided that: ''Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.''

DATA REQUIREMENTS FOR DRUGS AND BIOLOGICS

Section 118 of Pub. L. 105–115 provided that: ''Within 12 months after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall issue guidance that describes when abbreviated study reports may be submitted, in lieu of full reports, with a new drug application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and with a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262) for certain types of studies. Such guidance shall describe the kinds of studies for which abbreviated reports are appropriate and the appropriate abbreviated report formats.''

REQUIREMENTS FOR REVIEW OF APPROVAL PROCEDURES AND CURRENT GOOD MANUFACTURING PRACTICES FOR POSITRON EMISSION TECHNOLOGY

Section 121(c) of Pub. L. 105–115 provided that:

''(1) PROCEDURES AND REQUIREMENTS.—

''(A) IN GENERAL.—In order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs, not later than 2 years after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services shall establish—

''(i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and

''(ii) appropriate current good manufacturing practice requirements for such drugs.

''(B) CONSIDERATIONS AND CONSULTATION.—In establishing the procedures and requirements required by subparagraph (A), the Secretary of Health and Human Services shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs. Prior to establishing the procedures and requirements, the Secretary of Health and Human Services shall consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use positron emission tomography drugs.

''(2) SUBMISSION OF NEW DRUG APPLICATIONS AND ABBREVIATED NEW DRUG APPLICATIONS.—

''(A) IN GENERAL.—Except as provided in subparagraph (B), the Secretary of Health and Human Services shall not require the submission of new drug applications or abbreviated new drug applications under subsection (b) or (j) of section 505 (21 U.S.C. 355), for compounded positron emission tomography drugs that are not adulterated drugs described in section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) (as amended by subsection (b)), for a period of 4 years after the date of enactment of this Act [Nov. 21, 1997], or for 2 years after the date on which the Secretary establishes procedures and requirements under paragraph (1), whichever is longer.

''(B) EXCEPTION.—Nothing in this Act [see Short Title of 1997 Amendment note set out under section 301 of this title] shall prohibit the voluntary submission of such applications or the review of such applications by the Secretary of Health and Human Services. Nothing in this Act shall constitute an exemption for a positron emission tomography drug from the requirements of regulations issued under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)).''

''COMPOUNDED POSITRON EMISSION TOPOGRAPHY DRUG'' DEFINED

Section 121(e) of Pub. L. 105–115 provided that: ''As used in this section [amending sections 321 and 351 of this title and enacting provisions set out as notes under this section and section 351 of this title], the term 'compounded positron emission tomography drug' has the meaning given the term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).''

REQUIREMENTS FOR RADIOPHARMACEUTICALS

Section 122 of Pub. L. 105–115 provided that:

''(a) REQUIREMENTS.—

''(1) REGULATIONS.—

''(A) PROPOSED REGULATIONS.—Not later than 180 days after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services, after consultation with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry, shall issue proposed regulations governing the approval of radiopharmaceuticals. The regulations shall provide that the determination of the safety and effectiveness of such a radiopharmaceutical under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) shall include consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component of the radiopharmaceutical), and the estimated absorbed radiation dose of the radiopharmaceutical.

''(B) FINAL REGULATIONS.—Not later than 18 months after the date of enactment of this Act, the Secretary shall promulgate final regulations governing the approval of the radiopharmaceuticals.

''(2) SPECIAL RULE.—In the case of a radiopharmaceutical, the indications for which such radiopharmaceutical is approved for marketing may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.

''(b) DEFINITION.—In this section, the term 'radiopharmaceutical' means—

''(1) an article—

''(A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and

''(B) that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

''(2) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article.''

SPECIAL RULE

Section 123(f) of Pub. L. 105–115 provided that: ''The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).''

TRANSITION

Section 125(d) of Pub. L. 105–115 provided that:

''(1) IN GENERAL.—An application that was approved by the Secretary of Health and Human Services before the date of the enactment of this Act [Nov. 21, 1997] for the marketing of an antibiotic drug under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357), as in effect on the day before the date of the enactment of this Act, shall, on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of such Act (21 U.S.C. 355(b)) and approved for safety and effectiveness under section 505(c) of such Act (21 U.S.C. 355(c)), except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of such Act (21 U.S.C. 355(j)).

''(2) EXCEPTION.—The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act [Nov. 21, 1997]:

''(A)(i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and

''(ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and

''(B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations 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.

''(3) PUBLICATION.—For purposes of this section, the Secretary is authorized to make available to the public the established name of each antibiotic drug that was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) before the date of enactment of this Act [Nov. 21, 1997].''

TERMINATION OF ADVISORY PANELS

Advisory panels established after Jan. 5, 1973, to terminate not later than the expiration of the 2-year period beginning on the date of their establishment, unless, in the case of a panel established by the President or an officer of the Federal Government, such panel is renewed by appropriate action prior to the expiration of such 2-year period, or in the case of a panel established by Congress, its duration is otherwise provided for by law. See sections 3(2) and 14 of Pub. L. 92–463, Oct. 6, 1972, 86 Stat. 770, 776, set out in the Appendix to Title 5, Government Organization and Employees.

APPEALS TAKEN PRIOR TO OCTOBER 10, 1962

Section 104(d)(3) of Pub. L. 87–781 made amendments to subsec. (h) of this section inapplicable to any appeal taken prior to Oct. 10, 1962.

SECTION REFERRED TO IN OTHER SECTIONS

This section is referred to in sections 321, 331, 333, 334, 335a, 352, 353, 353a, 355a, 355b, 356, 356–1, 356a, 356c, 360, 360b, 360j, 360aa to 360ee, 360aaa, 360bbb, 360bbb–1, 374, 379g, 379h, 379i, 379r, 381, 382, 384, 802, 811, 827 of this title; title 10 section 1107; title 26 section 45C; title 28 section 2201; title 35 sections 155A, 156, 271; title 42 sections 236, 262, 282, 284m, 300cc–12, 300cc–13, 300cc–17, 1395y, 1396r–8.

§ 355a. Pediatric studies of drugs

(a) Definitions

As used in this section, the term ''pediatric studies'' or ''studies'' means at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used.

(b) Market exclusivity for new drugs

If, prior to approval of an application that is submitted under section 355(b)(1) of this title, the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) of this section