ORAL ARGUMENT NOT YET SCHEDULED

No. 08-5141

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

TEVA PHARMACEUTICALS USA INC.,
Plaintiff-Appellee,

v.

MICHAEL O. LEAVITT, Secretary of Health and Human Services, *et al.*,
Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BRIEF FOR THE APPELLANTS

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Certificate As To Parties, Rulings, And Related Cases

A. Parties

1. Plaintiff-Appellee:

The plaintiff below was Teva Pharmaceuticals USA, Inc.

2. Defendants-Appellants:

The defendants below were Michael O. Leavitt, Secretary of Health and Human Services; Andrew C. von Eschenbach, Commissioner of Food and Drugs; and the Food and Drug Administration.

3. Intervenors and Amici:

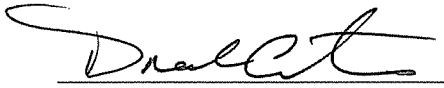
The intervenor-defendant below was Mylan Pharmaceuticals, and there were no amici.

B. Ruling Under Review

The ruling at issue on appeal is a final order entered April 11, 2008, by the United States District Court for the District of Columbia (Judge Royce C. Lamberth), Civ. No. 08-395. The opinion, entered from the bench, appears in the joint appendix at JA21-JA27. The final order appears at JA 28-29.

C. Related Cases

Counsel for the appellants are unaware of any related cases.



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Glossary

ANDA	—	Abbreviated new drug application
APA	—	Administrative Procedure Act
FDA	—	Food and Drug Administration
FDCA	—	Federal Food, Drug, and Cosmetic Act
JA	—	Joint Appendix
MMA	—	"The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003," Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003)
NDA	—	New drug application
Orange Book	—	"Approved Drug Products With Therapeutic Equivalence Evaluations"

Jurisdictional Statement

Teva Pharmaceuticals USA, Inc. ("Teva") brought this case under the Administrative Procedure Act ("APA"), and invoked district court jurisdiction under 28 U.S.C. § 1331. JA 7-20. The district court (J. Royce C. Lamberth) entered a final order disposing of all claims in favor of Teva on April 11, 2008. JA 28. The government filed a timely notice of appeal from the final order on May 16, 2008. JA 30-31. See Fed. R. App. P. 4(a). This Court has appellate jurisdiction over this appeal under 28 U.S.C. § 1291.

Statement of the Issue

The Federal Food, Drug, and Cosmetic Act ("FDCA") allows a generic drug manufacturer to qualify for 180-day marketing exclusivity only if it is first to file a paragraph IV certification to a patent that "claims" the innovator (brand-name) drug or "claims a use" of the brand-name drug and "for which information is required to be filed" under the statute. In this case the brand-name manufacturer withdrew the patent before Teva submitted its paragraph IV certification. The issue here is whether the district court improperly invalidated the Food and Drug Administration's ("FDA's") conclusion that Teva is not entitled to 180-day exclusivity based on certification to a patent that the innovator had withdrawn before any certification, and which therefore no longer "claimed" the drug at the time Teva submitted its certification.

Statutes and Regulations

The statutes and regulations most pertinent to this appeal are set forth in the statutory and regulatory addendum attached hereto.

Statement of the Case

I. Nature of the Case

This case involves the provision of the FDCA that authorizes the FDA to award in certain circumstances a period of 180 days of market exclusivity to a generic drug manufacturer. See 21 U.S.C. § 355(j)(5)(B)(iv). A generic drug manufacturer is eligible for a period of generic marketing exclusivity only if it is the first to file a "paragraph IV certification" (explained more fully below) in its abbreviated new drug application ("ANDA"), certifying that its generic drug product will not infringe a patent listed by the innovator drug company, or that the patent is invalid or unenforceable. See generally Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1064 (D.C. Cir. 1998).[1] A paragraph IV certification must be to a

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[1] Congress amended 21 U.S.C. § 355(j) in late 2003. See The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) ("MMA"). These amendments do not apply to the exclusivity determination in this case because Teva's ANDA was submitted before the December 8, 2003, enactment date of the MMA. See id. § 1102(b)(1). This brief refers to the pre-MMA version of the statute, and the 2001 version of the statute is the one in the statutory addendum.

patent that "claims the listed drug" or "claims a use for such listed drug" and "for which information is required to be filed" under the statute. 21 U.S.C. § 355(j)(2)(A)(vii).

In this case, before Teva filed its paragraph IV certification, the NDA holder withdrew the patent for which Teva now claims exclusivity and so notified FDA in writing; FDA updated its searchable, publicly-available, electronic database to reflect this withdrawal. This database, the electronic Orange Book (officially titled "Approved Drug Products With Therapeutic Equivalence Evaluations") is, and at all times relevant to this dispute was, available via FDA's website, www.fda.gov. The effect of the withdrawal of the patent was to render the patent unavailable as a basis for certification because the patent no longer "claimed" the drug or use of the drug and patent information no longer had to be filed for it. At the time Teva submitted its ANDA containing a paragraph IV certification, although the patent withdrawal was reflected in the electronic Orange Book, it was not reflected in FDA's paper Orange Book. This paper listing is the basis of Teva's claim (and the district court's holding) that Teva is entitled to the 180-day exclusivity period.

In 2001, when Teva filed its paragraph IV certification to the withdrawn patent, FDA informed Teva that the patent had been withdrawn and that Teva's

certification was improper; Teva immediately removed its certification to that patent. Six years later, Teva filed a citizen petition with FDA, claiming that FDA had improperly required Teva to remove the certification to the withdrawn patent. FDA denied Teva's citizen petition on February 26, 2008, noting that the statute requires a certification to a patent that "claims" the drug, and that FDA refers to the "most recent patent information submitted" in making the determination of whether a patent claims the drug. JA 78 n.14.

II. Course of Proceedings and Disposition Below

Teva challenged FDA's decision in its complaint and motion for preliminary injunction filed on March 4, 2008, seeking a declaration that the '952 patent be relisted and that Teva is entitled to exclusivity based on its paragraph IV certification to that patent. Mylan Pharmaceuticals, another risperidone ANDA applicant, intervened as a defendant on March 20, 2008.[2] The district court held a hearing on April 4, 2008, and consolidated Teva's motion for a preliminary injunction with the merits.

In its April 11, 2008, decision issued from the bench, the court granted judgment in favor of Teva. The court held that FDA's delisting of the patent from the electronic Orange Book was "unlawful" and that FDA's actions were arbitrary

[2] Mylan is not participating in this appeal.

and capricious. JA 21-27. The court reasoned that Teva had acted in accordance with statements in the paper Orange Book, and that Teva's paragraph IV certification was proper. JA 24. The district court did not address the language of the statute; i.e., whether Teva had certified to a patent that claimed the drug and for which information was required to be filed. The court ordered FDA to relist the '952 patent and restore Teva's paragraph IV certification, and enjoined FDA from approving any other ANDAs for risperidone until Teva's 180-day exclusivity expired.

Pursuant to the district court's ruling, FDA has relisted the '952 patent. All ANDAs for risperidone must thus be amended to include paragraph IV certifications to the relisted patent and, accordingly, be subject to a stay of final approval until expiration of the 180-day period that commences on the first day of commercial marketing of Teva's generic product.

Because the district court's decision is currently the only obstacle to FDA's ability to approve *all* risperidone ANDAs on June 29, 2008, the agency filed a motion to expedite the appeal, which was not opposed and which the Court granted on June 11, 2008. FDA's motion noted that expedition was warranted because this case could become moot approximately 180 days after June 29, 2008, and because the sooner the Court resolves the issue presented (and assuming the

Court does so in FDA's favor), the sooner *full* generic competition can begin and the sooner the public can obtain the benefit of the lower costs associated with full competition.

Statement of Facts

The facts in this case are not in dispute. The reference listed drug for Teva's ANDA is Janssen Pharmaceutica's ("Janssen") Risperdal (risperidone) tablets (NDA 20-272). JA 74. The 1-mg, 2-mg, 3-mg, 4-mg, and 5-mg Risperdal tablets were approved in 1993. Id. The 0.25-mg and 0.5-mg strengths were approved in 1999. Id. After approval, Janssen submitted information to FDA on the '663 patent and the '952 patent (the patent at issue here) for listing in the Orange Book entry for Risperdal tablets. Id. The '663 patent expired on December 29, 2007, and pediatric exclusivity attached to that patent will expire on June 29, 2008. The '952 patent will expire on October 27, 2009. Id.

By letter dated April 4, 2001, Janssen's parent company, Johnson & Johnson, requested that FDA remove the '952 patent from the Orange Book listing for the 1-mg, 2-mg, 3-mg, and 4-mg Risperdal tablets. Id. By letter dated June 11, 2001, Johnson & Johnson informed FDA that its April 4, 2001, correspondence also should have requested delisting of the '952 patent for the 0.25-mg, 0.5-mg, and 5-mg Risperdal tablets, and requested removal of the '952 patent from the

Orange Book listing for these strengths. Id. In response to Johnson & Johnson's request, FDA modified its patent listing database on June 11, 2001, to remove the '952 patent from the entries for Risperdal tablets. The delisting of the '952 patent was reflected in the publicly available, electronic Orange Book shortly after June 29, 2001, and no later than July 20, 2001, the date of the next database update.[3] Id.

On August 28, 2001, more than a month after FDA removed the '952 patent from the electronic Orange Book, Teva submitted an ANDA for risperidone tablets. JA 75. The Teva ANDA contained a paragraph III certification to the '663 patent and a paragraph IV certification to the '952 patent. After reviewing Teva's application, FDA concluded that Teva had submitted a patent certification for a patent (the '952 patent) that no longer claimed the reference listed drug, Risperdal tablets, because, as noted above, the NDA holder had withdrawn the patent and FDA had removed it from the electronic Orange Book. Id. Accordingly, FDA requested that Teva submit a revised patent certification, which

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[3] The withdrawal of the patent was not reflected in the paper Orange Book until the 2002 annual edition (the annual edition is sometimes referred to as the Addendum) came out in early 2002 because, at the time relevant to the events at issue in this case, patent withdrawals appeared only in the electronic Orange Book and in annual editions of the paper Orange Book, not the cummulative monthly supplements of the paper Orange Book. JA 76 n.12.

Teva did by letter dated October 22, 2001. Teva's letter stated, with reference to the revised patent certification:

> U.S. Patent 5,158,952 with an expiration of October 27, 2009 has been officially delisted from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), therefore only U.S. Patent 4,804,663 with an expiration of December 29, 2007 remains. Please find enclosed a patent certification revised accordingly.

Id. The revised patent certification stated:

> Paragraph III Certification: The undersigned hereby certifies that to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion there is one listed patent which claims the reference drug Risperdal® Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg. U.S. Patent No. 4804663 Expiration December 29, 2007 . . . .

Id. On October 24, 2001, FDA issued a standard acknowledgment letter to Teva indicating that Teva's ANDA for risperidone tablets had been received for substantive review. Id.[4]

Nearly six years later, on August 3, 2007, Teva filed a citizen petition with FDA, requesting that FDA relist the '952 patent for the 0.25-mg, 0.5-mg, 1-mg,

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[4] As explained in FDA regulations, when an ANDA is submitted, FDA first reviews it to ensure that it is sufficiently complete to permit a substantive review. See 21 C.F.R. § 314.101. If an ANDA is incomplete when submitted, FDA does not simply reject or deny it, but typically communicates with the applicant to assure that the application is complete, ordinarily by telephone. Id. § 314.101(b)(3). Thus, FDA makes a distinction between when an application is received and when it is received for substantive review.

2-mg, 3-mg, and 4-mg strengths of Risperdal tablets. See JA 54-70. Teva also asked FDA to confirm that Teva's eligibility for 180-day exclusivity was not affected by FDA's removal of the '952 patent from the Orange Book, and to refrain from approving any other ANDAs for risperidone tablets until Teva's 180-days of exclusivity had expired. Id.

By letter dated February 26, 2008, FDA responded to Teva's citizen petition. JA 71-97. FDA explained that the '952 patent had been withdrawn before Teva submitted its ANDA to FDA, and declined Teva's request to relist the patent. JA 71, 76-77. The citizen petition response also noted that the fact of the delisting was publicly available via the electronic Orange Book before Teva submitted its ANDA; that FDA informed Teva of the delisting soon after Teva had submitted its ANDA; and that Teva had withdrawn its certification to the '952 patent. JA 76-77. FDA also stated that its filing review of ANDAs "routinely includes a determination of whether the patent certifications contained in the ANDA correspond to the patents *actually* listed for the reference listed drug, *as assessed by the most current patent information the Agency has received.*" JA 78 (emphasis added). FDA further explained that the case cited by Teva, Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006), for the proposition that FDA may not delist a patent once a paragraph IV certification has been submitted, was

distinguishable: In Ranbaxy, the NDA holder's request to delist came almost two years *after* the ANDAs and paragraph IV certifications had been submitted, whereas in this case the patent was withdrawn and removed from the electronic Orange Book before Teva submitted is ANDA. Id. FDA's citizen petition response concluded that because "Teva's ANDA did not contain a paragraph IV certification for a listed patent, . . . Teva would not be eligible for 180-day exclusivity." JA 71-72.

Summary of Argument

The FDA decision challenged in this case was reasonable, consistent with the FDCA, and not arbitrary and capricious under the APA. The FDCA requires NDA holders to submit patents to FDA that "claim" drug products, and requires generic applicants to certify to such patents. See 21 U.S.C. §§ 355(b)(1); (j)(2)(A)(vii). The statutory provision that governs exclusivity, 21 U.S.C. § 355(j)(5)(B)(iv), refers to certification under 21 U.S.C. § 355(j)(2)(A)(vii), which pertains to certifications only to patents that "claim" the innovator drug and for which information is required to be filed under §§ 355(b) or (c). There is no question, and Teva does not appear to dispute, that at the time Teva submitted its ANDA, the '952 patent did not claim Risperdal because the innovator had withdrawn the patent. Thus, regardless of what appeared in the paper or electronic

Orange Book, under the language of the FDCA, Teva did not submit a certification to a patent that *claimed* Risperdal and no exclusivity can be based on such a certification.

The district court's ruling confuses the unequivocal statutory requirement that a generic applicant certify to a patent that "claims" a drug with the independent statutory language directing FDA to "publish" – in an unspecified format – the patent number and expiration date for any patent that claims the drug or use of the drug. Regardless of whether FDA did or did not properly remove the '952 patent from the paper Orange Book, there is no dispute that at the time Teva submitted its ANDA, the '952 patent no longer claimed Risperdal. Thus, Teva could not have submitted a certification to a patent that claimed the innovator drug and is not eligible for exclusivity, and the district court's ruling to the contrary was in error and should be reversed.

Alternatively, even if FDA's published list (rather than whether the patent actually claimed the drug at the time of Teva's certification) were dispositive, FDA reflected withdrawal of the patent at issue on a list of patents made available to the public before Teva erroneously certified to it. The FDCA requires FDA to "publish" patent information, which, at the time relevant to this case, FDA did in both electronic and print form. Neither the statute nor the regulation refers to a

paper listing of patents (or even requires a paper version), and FDA decided to maintain both a paper and electronic list, in part to provide industry with patent information as quickly as possible. Also, neither the statute nor the regulations refer to the manner in which FDA publicizes withdrawals. Even though the district court referred repeatedly to FDA having violated its "procedures," there were no "procedures" that specified how FDA was supposed to publicize withdrawn patents or that specified that a withdrawn patent removed from the electronic Orange Book but still listed in the paper Orange Book in fact "claims" the relevant product. Significantly, Teva has not argued in this case that it was unaware of the electronic Orange Book in 2001, and its rapid acquiescence to FDA's request in 2001 that it change its certification demonstrates the reasonableness of FDA's actions.

Standard of Review

The district court review of FDA's decision involved a question of law. Marshall County Health Care Auth. v. Shalala, 988 F.2d 1221, 1226 (D.C. Cir. 1993), and this Court's review of this legal issue is de novo. See, e.g., Fund for Animals, Inc. v. Kempthorne, 472 F.3d 872, 876 (D.C. Cir. 2006).

Argument

The District Court Erred In Finding FDA's Decision, Which is Consistent with The FDCA, To Be Unlawful

I. Review Under the APA

Under the APA, an agency decision may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. 706(2)(A). This standard is highly deferential to the agency. Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971).

When the Court is reviewing an agency's construction of statutory provisions, it is governed by the two-step analysis of Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984). First, the Court must inquire "whether Congress has directly spoken to the precise question at issue;" if Congress's intent is clear, the Court "must give effect to [such] unambiguously expressed intent." Id. at 842-43. Formulated another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." Barnhart v. Walton, 535 U.S. 212, 218 (2002). When Congress has not "directly" addressed "the precise question at issue," the Court may not "impose its own construction on the statute." Chevron, 467 U.S. at 843. Rather, it must determine if the agency's interpretation is based on "a permissible construction of the

statute." Id. Chevron deference is appropriate when "the interstitial nature of the legal question, the related expertise of the Agency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the Agency has given the question over a long period of time all indicate that Chevron provides the appropriate legal lens through which to view the legality of the Agency interpretation here at issue." Barnhart, 535 U.S. at 222. Thus, deference is appropriate in the drug approval context because of "the complexity of the statutory regime" and "FDA's expertise." Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1280 (D.C. Cir. 2004).

Accordingly, the D.C. Circuit has repeatedly given Chevron deference to FDA's interpretation of the FDCA and its implementing regulations. See, e.g., Novartis Pharms. Corp. v. Leavitt, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference, as do its interpretations of its own regulations unless plainly erroneous or inconsistent with the regulations."); Mylan v. Thompson, 389 F.3d at 1281; Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 883 (D.C. Cir. 2004); Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1319, 1320 (D.C. Cir. 1998) (citing Auer v. Robbins, 519 U.S. 452, 461 (1997)). See also Apotex, Inc. v. Thompson, 347 F.3d 1335, 1352 (Fed. Cir. 2003) ("Deference is due to an administrative agency's

regulations particularly when the subject matter of the regulatory authority is a 'highly detailed' regulatory program to which the agency has brought its 'specialized expertise,' . . . a characterization that aptly describes the FDA's role in the context of the regulatory scheme created pursuant to the Hatch-Waxman Act." (quoting United States v. Mead Corp., 533 U.S. 218, 235 (2001)).

For this reason, FDA's decisions about whether patents claim listed products, where patent information may be published, and what information FDA may rely on when reviewing ANDAs are entitled to considerable deference.

II. Statutory and Regulatory Framework

A. New Drug Applications

Under the FDCA, pharmaceutical companies seeking to market new drugs must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. §§ 355(a), (b). With the filing of its application, the NDA applicant must also submit "the patent number and the expiration date of any patent which claims the drug . . . or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted" against an unauthorized party. 21 U.S.C. § 355(b)(1). After a new drug application is approved, the NDA holder continues to have an obligation to submit

information for patents that claim its drug in the event new patents are issued. 21 U.S.C. § 355(c)(2). FDA must publish the patent information the NDA holder submits. 21 U.S.C. §§ 355(b)(1), (c)(2); see also 21 C.F.R. § 314.53(e). The statute and regulation require the NDA holder to submit, and in turn FDA to publish, only the patent number and expiration date. There is no statutory requirement dictating the manner in which FDA publishes patent withdrawals, and thus nothing limiting the manner of – or speed with which – FDA notifies the public that a patent has been withdrawn and therefore no longer claims the drug. See 21 U.S.C. §§ 355(b)(1), (c)(2). At the time relevant to this case, FDA published the Orange Book both electronically and in print.[5]

The obligation of an NDA filer to provide information about patents that "claim" the drug or the use of the drug arises when the NDA is filed, and therefore before FDA knows about such patents, or could ever have included such patents in any list. Whether a patent "claims" the drug is not the *result* of being listed in the Orange Book; that is a determination made by the NDA holder *before* a patent is included in the Orange Book.

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[5] Both the electronic and print versions of the Orange Book are entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," and thus both meet the definition of "the list" contained in 21 C.F.R. § 314.3(b).

B. Abbreviated New Drug Applications

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments"), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156, 271, and 282, an ANDA may be filed for a generic drug that relies, in part, on FDA's approval of a brand-name or "listed" drug.[6] 21 U.S.C. § 355(j). ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of the generic product, as does an NDA. See 21 U.S.C. § 355(j). Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective, and the FDCA sets forth in detail the information an ANDA must contain. See 21 U.S.C. § 355(j)(2)(A). The timing for approval of ANDAs depends, in part, on the patents submitted by the NDA holder for the innovator drug.

Each ANDA must contain at least one of the following four types of patent certifications for each patent that "claims the listed drug" or that "claims a use for such listed drug for which the applicant is seeking approval" and "for which information is required to be filed" by the NDA holder under the statute:

> (I) that the required patent information related to such patent has not been filed;

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[6] FDA has defined the "listed drug" to mean the approved new "drug product." 21 C.F.R. § 314.3(b).

(II) that such patent has expired;
(III) that such patent will expire on a particular date; or
(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

21 U.S.C. § 355(j)(2)(A)(vii).

An ANDA applicant that submits a paragraph IV certification must provide notice of the filing of its ANDA to the patent owner and to the holder of the NDA for the listed drug. 21 U.S.C. § 355(j)(2)(B)(I). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement, 35 U.S.C. § 271(e)(2)(A), thus enabling the NDA holder and patent owner to sue the ANDA applicant for patent infringement based solely on the filing of such a certification.

FDA may approve an ANDA with a paragraph IV certification, and the approval may become effective immediately despite the unexpired patent, unless an action for patent infringement is brought against the ANDA applicant within 45 days of the date the patent owner and NDA holder receive notice of the paragraph IV certification. 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(f)(2). If a patent action is brought, approval of the ANDA is automatically stayed until at least 30 months from the date that the patent owner and NDA holder received notice, unless a final decision is reached earlier in the patent case or the court

otherwise orders a longer or shorter period. 21 U.S.C. § 355(j)(5)(B)(iii).

As an incentive to the first generic drug manufacturer to expose itself to the risk of patent litigation, the statute provides that the manufacturer who files an ANDA containing the first paragraph IV certification to a patent that claims the drug or use of the drug is eligible for 180 days of marketing exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv). See Mova Pharm. Corp., 140 F.3d at 1064. The 180-day exclusivity provision at all times relevant to the events at issue here states:

> 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 [containing] 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 * * * holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier. See 21 U.S.C. §§ 355(j)(5)(B)(iv); 21 C.F.R. § 314.107(c)(1) & (2). The first date is known as the "commercial marketing" trigger, the second as the "court decision" trigger. The 180-day exclusivity period, therefore, begins on the date of the first commercial marketing of the generic drug or on the date of a court decision finding the patent covering the innovator drug invalid,

unenforceable, or not infringed, whichever occurs first.

The statute is clear that in the absence of an ANDA containing a proper paragraph IV certification, no ANDA applicant can obtain 180-day exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv). A paragraph IV certification can be submitted only to a patent that "claims the listed drug" or that "claims a use for such listed drug for which the applicant is seeking approval" and for which information is required to be submitted. 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). Absent such a patent, there can be no statutory exclusivity based on a paragraph IV certification.

C. Listing of Patent Information

From 1984 until 1998, FDA published the Orange Book in paper form only. However, in 1998, it also began to publish the Orange Book electronically on the Internet. JA 73. In 2001, patent information submitted to FDA between monthly supplements was placed on public display at FDA when received, but did not appear in either the paper or electronic version of the Orange Book until the next monthly supplement. 21 C.F.R. § 314.53(e). Both the paper Orange Book and the paper Cumulative Supplement referred users to the electronic Orange Book. JA 40-41, 76-77. The inside cover of the paper Addendum noted that the Orange Book is updated by monthly supplements and on the Internet. JA 77. Each

Cumulative Supplement referred in turn to the availability of the electronic Orange Book. JA 40-41, 76-77.

FDA publishes patent information in the Orange Book only for the approved aspects of a drug product. 21 U.S.C. §§ 355(b)(1) & (c)(2); 21 C.F.R. § 314.53(e). See also Pfizer, Inc. v. FDA, 753 F. Supp. 171 (D. Md. 1990) (NDA holders may submit to FDA for listing only patents covering the approved drug product). Specifically, patents submitted for an approved drug product must satisfy two separate criteria. The patent (1) must claim the approved drug product or a method of using the approved drug, and (2) must be one 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 product. 21 U.S.C. §§ 355(b)(1) & (c)(2); 21 C.F.R. § 314.53(b). Once an NDA is approved, the applicant must amend the patent submission to list only those patents that meet the listing criteria for the approved drug product. For example, an applicant may not receive approval for all aspects of the drug described in the original NDA submission, and thus not all of the patents submitted with the application will claim the drug product actually approved. 21 C.F.R. § 314.53(c)(2)(ii). In addition, patents obtained after an NDA is approved are to be submitted to FDA. See 21 U.S.C. § 355(c)(2).

FDA has long maintained that its has neither the expertise nor the resources to resolve patent issues and does not make independent determinations of the merits or applicability of patent claims. 59 Fed. Reg. 50338, 50342-43, 50345, 50349, 50352 (1994). This ministerial role in the listing process has been upheld. Apotex, Inc. v. Thompson, 347 F.3d at 1347-49; aaiPharma, Inc. v. Thompson, 296 F.3d 227, 241-43 (4th Cir. 2002); Alphapharm Pty Ltd. v. Thompson, 330 F. Supp. 2d 1, 7-9 (D.D.C. 2004). This ministerial role applies to both the listing and delisting of patents.

Neither the statute nor FDA regulations limit the listing of patents to a paper version. The statute simply requires FDA to "publish" the patent number and expiration date, and does not specify that the publication must be on paper only. 21 U.S.C. §§ 355(b)(1) & (c)(2). The regulation, 21 C.F.R. § 314.53(e), refers to publication of a "list," and again does not specify that this list must be only on paper. Additionally, nothing in the statute or regulation indicates the manner in which FDA is to publicize information regarding patent withdrawals. As noted above, FDA's regulation contemplates that newly-submitted patents are put on public display at FDA even before they appear in any form of the Orange Book, and FDA requires certification to such patents. Id.; JA 78 n.14.

III. FDA Properly Denied Teva's Request for Exclusivity Because Teva Did Not Certify to a Patent that Claimed The Brand-Name Drug Product

As explained above, if an ANDA applicant wishes to challenge the validity of a patent, or to claim that the patent would not be infringed by the product covered by the ANDA, the applicant must submit a paragraph IV certification. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This case turns on the statutory language providing that the patent that is the subject of the certification must be one "which claims the listed drug" or "which claims a use for such listed drug for which the applicant is seeking approval" and for which patent information is required to be submitted under the statute. 21 U.S.C. § 355(j)(2)(A)(vii). If there is no patent that claims the listed drug, or claims a use for the listed drug, there can be no valid certification, and without a valid paragraph IV certification, Teva cannot claim exclusivity.

In the proceeding below, Teva did not appear to dispute that the '952 patent had in fact been withdrawn by the patent holder, nor did Teva appear to dispute that this fact was reflected in the electronic Orange Book. It instead argued that these facts were "legally immaterial." Teva's Memorandum in Support of its Motion for a Preliminary Injunction at 21. In addition, although the district court

acknowledged that the withdrawal of the '952 patent was reflected in the electronic Orange Book, the court stated that such delisting was irrelevant and unlawful. JA 25. The district court did not analyze the exclusivity provisions of the statute. The district court disagreed with FDA's decision – not on the basis that the patent at issue actually "claimed" the drug as required by the statute, but on the ground that FDA had violated a supposed independent obligation to provide an updated paper list of patent withdrawals. Notably, the district court did not find – nor could it, given that the brand-name company had withdrawn the patent at issue – that the patent to which Teva certified "claimed" Risperdal.

The central question before the district court was whether a patent that has been withdrawn by the NDA holder may still claim the innovator drug product for purposes of determining exclusivity. The district court apparently believed that as long as a patent appears in the paper Orange Book at the time a paragraph IV certification is filed, that patent may serve as the basis for a period of generic exclusivity even if the NDA holder has withdrawn the patent and this withdrawal is reflected in the electronic Orange Book. See JA 24-25. The court's view is inconsistent with the statute. As noted above, a patent that has been withdrawn by the NDA holder does not "claim" the drug product. The FDCA provides that ANDA applicants must certify to patents that "claim" the innovator drug, 21

U.S.C. § 355(j)(2)(A)(vii), and also provides that FDA must "publish" certain patent information which FDA does both electronically and in print in the Orange Book, 21 U.S.C. § 355(b)(1). These two requirements, however, are not inexorably linked and it is only the former – certifying to a patent that claims the innovator drug – that is a statutory prerequisite to receiving 180-days of exclusivity.

The district court stated that FDA's "own procedures" require that an ANDA applicant search the paper Orange Book to determine the proper patent certifications to submit with its ANDA. JA 24-25. In fact, there is no requirement anywhere in the FDCA or FDA's regulations that an ANDA applicant search any version of the Orange Book. Rather, the statute requires ANDA applicants to submit a patent certification for any patent that claims the listed drug and for which information is required to be filed with FDA. 21 U.S.C. § 355(j)(2)(A)(vii). Although most ANDA applicants can and do obtain patent information by searching both the paper and electronic Orange Book, the statute mandates only that an appropriate certification be submitted for patents that claim the listed drug; that requirement is not inexorably linked to listings in the (paper or electronic) Orange Book. Nor is there anything in the statute or regulations about "procedures" for publicizing the withdrawal of patents by the NDA holder. As

FDA carefully explained in its response to Teva's citizen petition, its "procedure" is to utilize the most current information available to the agency about what patents the NDA holder asserts claim the listed drug when analyzing what certifications are required or permitted in an ANDA. JA 76-78.

The only basis for Teva's complaint (and the district court holding) is that the '952 patent appeared in the paper Orange Book at the time of Teva's certification, and language in the paper Orange Book stated that changes in patent listings are reflected in the paper Orange Book. Thus, the 2001 Orange Book stated: "The patent numbers and the expiration dates of appropriate patents claiming drug products that are the subject of approved applications will be published in this Addendum or in the monthly Cumulative Supplement to this publication." JA 34. The 2001 Cumulative Supplement stated that it was intended to provide, "among other things, information on newly approved drugs and, if necessary, revised therapeutic equivalence evaluations and updated patent and exclusivity data." JA 37. Although these references in the paper Orange Book relied on by Teva indicate that the electronic and paper versions of the Orange Book would be updated concurrently, see JA 40, that was not the case in 2001 with patent withdrawals. At that time, patent withdrawals were reflected in the monthly update to the electronic Orange Book, but not the paper monthly

cumulative supplements. JA 76 n.12.

However, the paper Orange Book itself refers to the electronic version of the patent listing. The inside cover notes that the Orange Book is updated by monthly supplements and on the Internet. JA 77. Each Cumulative Supplement refers in turn to the availability of the electronic Orange Book. JA 40, 76.[7] Most importantly, however, the Orange Book statements that form the basis of Teva's case are not the law, nor do they change the law regarding whether a patent "claims" a drug. See, e.g., Schweiker v. Hansen, 450 U.S. 785, 789 (1981) ("[T]he Claims Manual is not a regulation. It has no legal force, and it does not bind the SSA."); Chiron Corp. and PerSeptive Biosystems, Inc. v. NTSB, 198 F.3d 935, 943 (D.C. Cir. 1999) ("the Guidance is not a source of law . . . it . . . gives information, not rights. . . . not every 'piece of paper emanating from a Department or Independent Agency is a regulation.'") (quoting in part Piccone v. United States, 407 F.2d 866, 877 (Ct. Cl. 1969)); Molycorp v. EPA, 197 F.3d 543, 546 (D.C. Cir. 1999) (a Technical Background Document, which was intended to

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[7] Since 2005, the Orange Book has stated that interested parties should consult the electronic Orange for updated patent information. JA 53. This change in 2005, however, does not mean that in 2001 the '952 patent actually "claimed" Risperdal after its withdrawal by Johnson & Johnson because it remained in the paper Orange Book. Nor does it make FDA's method of ensuring compliance with the statute in 2001 unreasonable or in violation of the APA.

give information to the public, "is not a substitute for . . . legal requirements; nor is it a regulation itself."); Professionals and Patients for Customized Care v. Shalala, 56 F.3d 592 (5th Cir. 1995) (FDA Compliance Policy Guide not a substantive rule); Brock v. Cathedral Bluffs Shale Oil Co., 796 F.2d 533, 538 (D.C. Cir. 1986) (the Secretary of Labor's Enforcement Policy and Guidelines for Independent Contractors, which provided when, "as a general rule, a production-operator may be properly cited for a violation. . . ," was not a substantive regulation.); Farrell v. Dep't of the Interior, 314 F.3d 584, 590 (Fed. Cir. 2002) ("Table of Penalties" not binding on agency: "an agency statement, not issued as a formal regulation, binds the agency only if the agency intended the statement to be binding.").

The statements in the Orange Book relied on by Teva do not "control" the outcome of this case, as Teva argued below. Teva's Reply Memorandum in Support of its Motion for Expedited Injunctive Relief at 2, 6, 8, 10. What "controls" is the statute, specifically the provisions that require ANDA certifications only to patents that claim listed drug products for which information is required to be filed. Thus, the statements in the paper versions of the Orange Book directing applicants to search the paper supplements for updated patent information do not restrict FDA to considering only patent information appearing in the paper Orange Book when making exclusivity determinations, particularly

when the relevant statute and regulations are unequivocal that it is the actual status of the patent that controls, not FDA's paper description.

Whether a patent "claims" the drug determines whether FDA publishes the information on a list of patent information – not the other way around. As noted above, whether a patent "claims" the drug is not the *result* of appearing in the Orange Book. The continuing inclusion of a patent on FDA's list after the innovator has withdrawn a patent does not mean that the patent still claims the drug and therefore that FDA is compelled to require (or permit) ANDA applicants to certify to the patent and then to award exclusivity to the first applicant who does so. Indeed, any other rule would turn FDA's actions in publishing patents into a basis for estoppel against the government. FDA's decision that because the NDA holder had withdrawn the '952 patent it no longer claimed Risperdal is reasonable, and the district decision holding otherwise should be reversed.

IV. Even If FDA's Listing Of Patents Were Dispositive, FDA's Response to Teva's Citizen Petition was Proper Because the '952 Patent had Been Removed From the Electronic Orange Book Before Teva Submitted its ANDA to FDA

Even if this case turned on whether the '952 patent appeared on the list of patents FDA used to fulfill its obligation of publishing patent information, Teva would not be entitled to exclusivity. At the time of Teva's certification, FDA had

provided notice of the removal of the '952 patent through its electronic Orange Book. The agency's actions in this case therefore have been reasonable and not arbitrary and capricious.

In denying Teva's citizen petition, FDA explained that the fact of the delisting of the '952 patent was publicly available via the electronic Orange Book before Teva submitted its ANDA. JA 73, 76-78. FDA also stated that, when reviewing ANDAs, it conducts an independent review of the required patent certifications and uses "the most current patent information the Agency has received." JA 78. In 2001, Teva did not object to FDA's approach. Indeed, when FDA informed Teva that the patent had been delisted, Teva readily acquiesced and certified that "to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion" the '952 patent was not listed for Risperdal. JA 75. Teva removed its certification to the '952 patent and said nothing more about it for six years, until 2007.

As explained above, neither the statute nor the regulation refers to a paper listing of patents (or even requires a paper version). See 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53(e). There is nothing preventing FDA's use of electronic publication on the Internet to comply with the statute, and FDA's decision to do so is not arbitrary and capricious. To the contrary, FDA's decision to use the

electronic Orange Book to make patent information public as quickly as possible is entirely reasonable.

At no time during this litigation has Teva argued that at the time of its certification to the '952 patent it was unaware of the electronic Orange Book. The record in this case shows that other ANDA applicants were aware of the electronic Orange Book. For example, a different applicant submitted an ANDA for risperidone in November 2001; this ANDA contained a printout from the electronic Orange Book, dated October 30, 2001, showing that the only patent listed for Risperdal tablets was the '663 patent. See JA 77. This November 2001 ANDA contained a patent certification only to the '663 patent. Thus, others in the generic industry knew about, and relied on, the electronic Orange Book for patent information in 2001.

The district court stated that FDA conceded that the '952 patent was a "listed patent" at the time Teva submitted its ANDA. JA 23. It is unclear exactly what the court meant by "listed patent" but to the extent the court meant a patent listed in the Orange Book, the court is mistaken. FDA acknowledged that at the time Teva submitted its ANDA the '952 patent appeared in the paper Orange Book (both the annual edition and the cumulative supplement). However, because the patent had been withdrawn by the NDA holder and FDA had removed the patent

from the electronic Orange Book, FDA properly considered – and argued below – that the '952 patent was delisted before the date on which Teva submitted its ANDA. JA 71, 74-77. Therefore, Teva's certification to the '952 patent cannot be the basis for 180-day exclusivity.

Conclusion

For the foregoing reasons, the district court's judgment should be reversed, and consistent with this Court's June 11, 2008, order granting expedition, the government respectfully requests the Court to do so as promptly as possible in order to permit FDA to approve other ANDAs whose approvals will be delayed by the district court decision.

Respectfully submitted,

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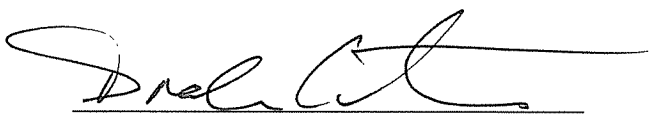
June 18, 2008

CERTIFICATE OF COMPLIANCE WITH RULE 32(a)

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 7,528 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Word Perfect 12 in Times New Roman 14 point typeface.



DRAKE CUTINI
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June 18, 2008

STATUTORY AND REGULATORY ADDENDUM

STATUTORY AND REGULATORY ADDENDUM

1 of 66 DOCUMENTS

*** ARCHIVE MATERIAL ***

*** THIS SECTION IS CURRENT THROUGH 107TH CONGRESS, 1ST SESSION ***

TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT
DRUGS AND DEVICES
DRUGS AND DEVICES

21 USCS § 355 (2001)

§ 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) 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). 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)--

(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) 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) 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 351 of the Public Health Service Act *[42 USCS § 262]*, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act *[42 USCS § 262]* 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 351 of the Public Health Service Act *[42 USCS § 262]* (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), 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) applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by a 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) could not be filed with the submission of an application under subsection (b) because the application was filed before the patent information was required under subsection (b) 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) 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 the date of the enactment of this sentence, and if the holder of an approved application could not file patent information under subsection (b) 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) 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) 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), 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), 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, United States Code* [*35 USCS § 271*(e)(4)(A)], 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, United States Code* [*28 USCS § 2201*], for a declaratory judgment with respect to the patent.

Any action brought under such section 2201 [*28 USCS § 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) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) 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).

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this clause [enacted Sept. 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) 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) before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under subsection (b) 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). 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) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause [enacted Sept. 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) 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) if the investigations described in clause (A) of subsection (b)(1) 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) is approved after the date of enactment of this clause [enacted Sept. 24, 1984] and the supplement contains reports of new clinical investigation (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 subsection (b) 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) if the investigations described in clause (A) of subsection (b)(1) 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) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this clause [enacted Sept. 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) 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 the date of enactment of this clause [enacted Sept. 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) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); 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 application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. 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) 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 this 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) with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) or to comply with the notice requirements of section 510(k)(2) [*21 USCS § 360*(k)(2)], 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) 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, United States Code*. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. 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 of the United States Code*. 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); 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 the date of the enactment of the Food and Drug Administration Modernization Act of 1997 [enacted Nov. 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 application for new drug approval; required information and certification; approval of application; hearing.

(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 201(p) [*21 USCS § 321*(p)], and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and 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);

(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)--

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

(II) that such patent has expired,

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

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

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

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

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

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

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

(ii) The notice referred to in clause (i) shall state that an application, which contains data for 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 201(p) [*21 USCS § 321*(p)],

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

(D) (i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage 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 of quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e), the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) for grounds described in the first sentence of subsection (e), the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (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 requirements 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 made effective on the last applicable date determined under the following:

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

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

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

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

(II) if before the expiration of such period the court decides that such patent has been infringed, the approval shall be made effective on such date as the court orders under *section 271(e)(4)(A) of title 35, United States Code* [*35 USCS § 271*(e)(4)(A)], 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, United States Code*, for a declaratory judgment with respect to the patent. Any action brought under section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

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

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

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

whichever is earlier.

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

(D) (i) If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or sale of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection [enacted Sept. 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).

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

(b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

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

(iv) If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection [enacted Sept. 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).

(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection [enacted Sept. 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 the date of enactment of this subsection [enacted Sept. 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) or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended--

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

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

(7) (A) (i) Within sixty days of the date of the enactment of this subsection [enacted Sept. 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) before the date of the enactment of this subsection [enacted Sept. 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) or approved under this subsection during the thirty-day period.

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

(B) A drug approved for safety and effectiveness under subsection (c) or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or the date of enactment [enacted Sept. 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) or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn

from sale for safety or effectivenss reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list--

(i) for the same period as the withdrawal or suspension under subsection (e) or paragraph (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 absored 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) 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) 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, or 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) 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) 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) which refers to such drug or upon the date upon which the approval of an application under subsection (j) 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 section 505 [this section] or section 351 of the Public Health Service Act *[42 USCS § 262],* the Secretary shall establish panels of experts or use panels of experts established before the date of enactment of the Food and Drug Administration Modernization Act of 1997 [enacted Nov. 21, 1997], or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 904 *[21 USCS § 394]* 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 Act 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 Act 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, United States Code*, 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.

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

HISTORY; ANCILLARY LAWS AND DIRECTIVES

References in text:

As used in subpara. (D) of subsec. (c)(3), the "date of the enactment of this subsection", probably refers to September 24, 1984, which is the date of enactment of such subparagraph.

For information as to the rate for "positions classified above grade GS-15 of the General Schedule", see *5 USCS § 5376.*

"This Act", referred to in this section, is Act June 25, 1938, ch 675, 52 Stat. 1040, which appears generally as *21 USCS §§ 301* et seq.

Explanatory notes:

The amendment made by § 1000(a)(9) of Act Nov. 29, 1999, P.L. 106-113, is based on § 4732(b)(11) of Chapter 2 of Subtitle G of Title IV of S. 1948 (113 Stat. 1501A-584), as introduced on Nov. 17, 1999, which was enacted into law by such § 1000(a)(9).

Effective date of section:

For the effective date of this section, see *21 USCS § 301* notes.

Amendments:

1960. Act June 11, 1960, in subsec. (g), inserted "or by certified mail".

1962. Act Oct. 10, 1962, in subsec. (a), inserted "an approval of"; in subsec. (b)(1), inserted "and whether such drug is effective in use"; substituted subsec. (c) for one which read: "An application provided for in subsection (b) shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application."; substituted subsec. (d) for one which read: "If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate test by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application issue an order refusing to permit the application to become effective."; substituted subsec. (e) for one which read: "The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis

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PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
SUBPART A -- GENERAL PROVISIONS

21 CFR 314.3

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

Abbreviated application means the application described under § 314.94, including all amendments and supplements to the application. "Abbreviated application" applies to both an abbreviated new drug application and an abbreviated antibiotic application.

Act means the Federal Food, Drug, and Cosmetic Act (sections 201-901 (21 U.S.C. 301-392)).

Applicant means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug or an antibiotic drug and any person who owns an approved application or abbreviated application.

Application means the application described under § 314.50, including all amendements and supplements to the application.

505(b)(2) Application means an application submitted under section 505(b)(1) of the act for a drug for which the investigations described in section 505(b)(1)(A) of the act 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.

Approvable letter means a written communication to an applicant from FDA stating that the agency will approve the application or abbreviated application if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application or abbreviated application and does not permit marketing of the drug that is the subject of the application or abbreviated application.

Approval letter means a written communication to an applicant from FDA approving an application or an abbreviated application.

Drug product means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.

FDA means the Food and Drug Administration.

Listed drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

Not approvable letter means a written communication to an applicant from FDA stating that the agency does not consider the application or abbreviated application approvable because one or more deficiencies in the application or abbreviated application preclude the agency from approving it.

Reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.

Right of reference or use means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

The list means the list of drug products with effective approvals published in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication.

HISTORY: [50 FR 7493, Feb. 22, 1985; 57 FR 17981, April 28, 1992]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:
21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e.

NOTES: NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.
Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:
[EDITORIAL NOTE: For nomenclature changes to chapter I see 59 FR 14366, Mar. 28, 1994.]
[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see 61 FR 67710, Dec. 24, 1996; 61 FR 68145, Dec. 27, 1996; 62 FR 49881, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:

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SUBPART B -- APPLICATIONS

21 CFR 314.53

§ 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted. An applicant described in paragraph (a) of this section shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Process patents are not covered by this section and information on process patents may not be submitted to FDA. For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application.

(c) Reporting requirements -- (1) General requirements. An applicant described in paragraph (a) of this section shall submit the following information for each patent described in paragraph (b) of this section:

(i) Patent number and the date on which the patent will expire.

(ii) Type of patent, i.e., drug, drug product, or method of use.

(iii) Name of the patent owner.

(iv) If the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and §§ 314.52 and 314.95.

(2) Formulation, composition, or method of use patents -- (i) Original declaration. For each formulation, composition, or method of use patent, in addition to the patent information described in paragraph (c)(1) of this section

the applicant shall submit the following declaration:

The undersigned declares that Patent No. _____ covers the formulation, composition, and/or method of use of (name of drug product). This product is (currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or_ (the subject of this application for which approval is being sought):

_____

(ii) Amendment of patent information upon approval. Within 30 days after the date of approval of its application, if the application contained a declaration required under paragraph (c)(2)(i) of this section, the applicant shall by letter amend the declaration to identify each patent that claims the formulation, composition, or the specific indications or other conditions of use that have been approved.

(3) No relevant patents. If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, it shall so declare.

(4) Authorized signature. The declarations required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) When and where to submit patent information -- (1) Original application. An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under § 314.60.

(2) Supplements. (i) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.

(3) Patent information deadline. If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of

the patent.

(4) Copies. The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., rm. 2-14, 12420 Parklawn Dr., Rockville, MD 20857. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) Submission date. Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(6) Identification. Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an application, "Time Sensitive Patent Information."

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857.

(f) Correction of patent information errors. If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Drug Information Services Branch (HFD-84), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holderwithdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

HISTORY: [59 FR 50363, Oct. 3, 1994]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:
21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e.

NOTES: [EFFECTIVE DATE NOTE: 59 FR 50363, Oct. 3, 1994, which added this section, became effective Nov. 2, 1994.]
NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.

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21 CFR 314.101

§ 314.101 Filing an application and receiving an abbreviated new drug application.

(a)(1) Within 60 days after FDA receives an application, the agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application apply, the agency will file the application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."

(3) If FDA refuses to file the application, the agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the application under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the agency's notification an informal conference with the agency about whether the agency should file the application. If, following the informal conference, the applicant requests that FDA file the application (with or without amendments to correct the deficiencies), the agency will file the application over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the application is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an application that is filed over protest. If FDA refuses to file the application under paragraph (e) of this section, the applicant may amend the application and resubmit it, and the agency will make a determination under this section whether it may be filed.

(b)(1) An abbreviated new drug application will be reviewed after it is submitted to determine whether the abbreviated application may be received. Receipt of an abbreviated new drug application means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the abbreviated new drug application not to have been received applies, the agency will receive the abbreviated new drug application and notify the applicant in writing.

(3) If FDA considers the abbreviated new drug application not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant, ordinarily by telephone. The applicant may then:

(i) Withdraw the abbreviated new drug application under § 314.99; or

(ii) Amend the abbreviated new drug application to correct the deficiencies; or

(iii) Take no action, in which case FDA will refuse to receive the abbreviated new drug application.

(c) [Reserved]

(d) FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:

(1) The application or abbreviated application does not contain a completed application form.

(2) The application or abbreviated application is not submitted in the form required under § 314.50 or § 314.94.

(3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and § 314.50 or § 314.94.

(4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(5) The application or abbreviated application does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliancewith the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved application or abbreviated application and the applicant of the submission:

(i) Has an approved application or abbreviated application for the same drug product; or

(ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

(e) The agency will refuse to file an application or will consider an abbreviated new drug application not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 et seq.) and subchapter F of this chapter.

(2) In the case of a 505(b)(2) application or an abbreviated new drug application, the drug product contains the same active moiety as a drug that:

(i) Was approved after September 24, 1984, in an application under section 505(b) of the act, and

(ii) Is entitled to a 5-year period of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act and § 314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the application or abbreviated application contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

(f)(1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the application; or

(ii) Issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the abbreviated new drug application. If FDA disapproves the abbreviated new drug application, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an abbreviated new drug application in response to a not approvable letter.

(3) This paragraph does not apply to applications or abbreviated applications that have been withdrawn from FDA review by the applicant.

HISTORY: [57 FR 17987, Apr. 28, 1992; 57 FR 29353, July 1, 1992; 59 FR 50366, Oct. 3, 1994; 62 FR 40570, 40599, July 29, 1997; 64 FR 396, 402, Jan. 5, 1999, as confirmed at 64 FR 26657, May 17, 1999]

AUTHORITY: AUTHORITY NOTE APPLICABLE TO ENTIRE PART:
21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e.

NOTES: [EFFECTIVE DATE NOTE: 64 FR 396, 402, Jan. 5, 1999, amended this section, effective May 20, 1999.]
NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.
Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:
[EDITORIAL NOTE: For nomenclature changes to chapter I see 59 FR 14366, Mar. 28, 1994.]
[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see 61 FR 67710, Dec. 24, 1996; 61 FR 68145, Dec. 27, 1996; 62 FR 49881, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:
[PUBLISHER'S NOTE: The authority citation for Part 314 was revised at 65 FR 64607, 64617, Oct. 30, 2000, effective Feb. 27, 2001. 66 FR 10815, Feb. 20, 2001, delayed the effective date of the amendment appearing at 65 FR 64607, 64617, Oct. 30, 2000, until Apr. 30, 2001. For the convenience of the user, the authority citation effective Apr. 30, 2001, has been set out below:
21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.]
[PUBLISHER'S NOTE: For Federal Register citations concerning Part 314 Clarifications, see 62 FR 63268, Nov. 28,

Certificate of Service

I hereby certify that I caused the Appellants' Brief and Joint Appendix to be served on this 18th day of June, 2008, upon the following by means of first class mail and email:

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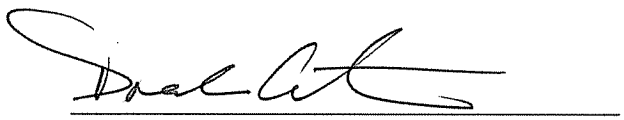

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