DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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[Docket No. 02N–0417]

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Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its patent listing requirements for new drug applications (NDAs). The proposal would clarify the types of patents that must and must not be listed and revise the declaration that NDA applicants must provide regarding their patents to help ensure that NDA applicants list only appropriate patents. The proposal would also revise the regulations regarding the effective date of approval for certain abbreviated new drug applications (ANDAs) and certain applications submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (505(b)(2) applications). In certain situations, Federal law bars FDA from making the approval of an ANDA or 505(b)(2) application effective for 30 months if the applicant certified that the patent claiming a drug is invalid or will not be infringed, and the patent owner or NDA holder brings suit for patent infringement. The proposal also would state that there will be only one

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opportunity for a 30-month stay in the approval date of each ANDA or 505(b)(2) application. The proposal is designed to make the patent listing process more efficient and to enhance the ANDA and 505(b)(2) application approval processes.

DATES: Submit written or electronic comments by [*insert date 60 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection requirements by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Jarilyn Dupont, Office of Policy, Planning, and Legislation (HFW–14), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3360.

SUPPLEMENTARY INFORMATION:

I. Background

A. What Is the Relationship Between Patent Listing, Patent Certification, and the Date of Approval for Certain Applications?

Title I of the Drug Price Competition and Patent Term Restoration Act (Public Law 98–417, 98 Stat. 1585 (1984) ("Hatch-Waxman amendments")) amended the act to authorize the approval of duplicate or "generic" versions

of approved drug products. Title I also amended section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) by requiring all NDA applicants to file, as part of the NDA, "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." Section 505(c)(2) of the act imposes a similar patent listing obligation on persons whose NDAs we have approved when the NDA holder could not have filed the patent information with its application (either because the application was filed before the act required NDA applicants to submit patent information or because the patent issued after we had approved the NDA).

We publish patent information in our approved drug products list entitled "Approved Drug Products With Therapeutic Equivalence Evaluations." The list is known popularly as the "Orange Book" because of its orange-colored cover.

The Hatch-Waxman amendments also require persons submitting a 505(b)(2) application or ANDA to make certifications regarding the listed patents pertaining to the drug which they intend to duplicate (see sections 505(b)(2)(A)(i) through (b)(2)(A)(iv) and 505(j)(2)(A)(vii)(I) through (j)(2)(A)(vii)(IV) of the act). In brief, these certifications state that:

- Patent information has not been filed;
- The patent has expired;
- The patent will expire on a specific date; or
- The patent is invalid or will not be infringed.

If the ANDA or 505(b)(2) application applicant certifies that the patent is invalid or will not be infringed (a certification known as a "paragraph IV"

certification because it is the fourth type of patent certification described in the act), the act requires the applicant to notify the patent owner and NDA holder (see sections 505(b)(3) and 505(j)(2)(B) of the act.) In general, the notice states that an abbreviated application has been submitted for the drug with respect to which the paragraph IV certification is made and also includes 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" (*id.*). If an action for patent infringement is brought within 45 days after the paragraph IV certification has been received, then we may not make the approval of an abbreviated application effective for 30 months, or such shorter or longer period as a court may order or the date of a court decision (see sections 505(c)(3)(C) and 505(j)(4)(B)(iii) of the act).

These statutory provisions reflect the Hatch-Waxman amendments' attempt to balance two competing interests: Promoting competition between "brand-name" and "generic" drugs and encouraging research and innovation. The act promotes competition by creating a process to expedite the filing and approval of ANDAs and 505(b)(2) applications and for resolving challenges to patents before marketing begins. At the same time, the act seeks to protect the patent owner's or NDA holder's interests by giving it the opportunity to list patents, to receive paragraph IV certifications, and to delay an ANDA's or 505(b)(2) application's effective date of approval during patent infringement litigation. (We will refer to the date the approval is made effective as the "approval date" throughout the remainder of this preamble.)

We published regulations pertaining to patent listing and patent certifications in the **Federal Register** on October 3, 1994 (59 FR 50338). The regulations regarding the submission of patent information are at §§ 314.50(h)

and 314.53 (21 CFR 314.50(h) and 314.53), while the patent certification requirements are at §§ 314.50(i) and 314.94(a)(12) for 505(b)(2) applications and ANDAs respectively.

B. What Events Led to This Proposal?

In recent years, we have seen NDA applicants list new patents shortly before other listed patents for the same drug product are scheduled to expire. Some listings, such as those for BuSpar (buspirone hydrochloride), Paxil (paroxetine hydrochloride), Tiazac (diltiazem hydrochloride), and Prilosec (omeprazole), have resulted in high profile litigation. (We discuss some of these cases in section II.A of this document.) A number of disputes over recently listed patents have addressed whether the patent meets the regulatory requirements for listing in the Orange Book and have sometimes resulted in decisions that are not entirely consistent with our regulatory policy or our interpretation of our regulations.

Additionally, on May 16, 2001, the Bureau of Competition and the Policy Planning Staff of the Federal Trade Commission (FTC) submitted a citizen petition (FDA docket number 01P–0248) (FTC Citizen Petition) that requested our guidance concerning the criteria that a patent must meet before it is listed in the Orange Book. The FTC Citizen Petition asked us to clarify several patent listing issues and indicated that FTC was conducting an extensive study of generic drug competition. FTC issued the study in July 2002, in a report entitled *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (FTC Report). The FTC Report focused on the procedures used to facilitate a generic drug's entry into the market before the expiration of a patent or patents that pertain to the brand-name drug product. The FTC Report noted that FTC had submitted a citizen petition to us. FTC also recommended that the law be

changed to "permit only one automatic 30-month stay per drug product per ANDA to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA" (see FTC Report at page ii). The FTC Report explained, "To permit only one 30-month stay per drug product per ANDA should eliminate most of the potential for improper Orange Book listings to generate unwarranted 30-month stays" (*id.* at page v (footnote omitted)). In an appendix to its report, FTC asked that we issue a regulation or guidance clarifying whether an NDA holder could list various types of patents in the Orange Book. The types of patents for which FTC sought clarification were patents that claimed metabolites, polymorphs, or intermediates, product by process patents, and double patents (see FTC Report at pages A–39–A–45).

II. Description of the Proposed Rule

Given these patent listing issues, the FTC citizen petition, and the FTC Report, we decided to issue this proposed rule to help NDA applicants and NDA holders determine whether specific patents must be submitted to us for listing and to help 505(b)(2) application applicants, ANDA applicants, and other interested parties determine whether a patent listing is proper. This proposed rule will address:

- The types of patents that must and must not be listed;
- The patent certification statement that NDA applicants must submit as part of an NDA, an amendment to an NDA, or a supplement to an NDA; and
- The 30-month stay in effective dates of approval for a 505(b)(2) application or an ANDA.

A. Proposed § 314.53(b)—What Patents Must Be Listed in the Orange Book?

1. *What Does the Current Regulation Say?*

Our patent listing regulation, at § 314.53, applies to persons submitting an NDA, an amendment to an NDA, or a supplement to an NDA. Section 314.53(b) describes the patents for which information must be submitted and states, in part, that the applicant:

> * * * shall submit information on each patent that claims 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.

Section 314.53 reflects the statutory provision that requires NDA applicants to file the patent number and 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" (see section 505(b)(1) of the act). Thus, both the act and our regulations establish two distinct criteria for a patent intended for listing in the Orange Book: (1) The patent must claim the approved drug product or a method of using the approved drug product; and (2) the patent must be one with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner sought to engage in the drug's manufacture, use, or sale.

2. *How Have We Interpreted the Regulation?*

As we mentioned earlier in section I.B of this preamble, the FTC Citizen Petition sought our guidance on whether an NDA holder can list a patent claiming an unapproved aspect of an approved drug. The petition maintained that the act and our regulations do not allow listing of a patent that claimed "only an unapproved component, an unapproved formulation, or an unapproved use of a drug product" (see FTC Citizen Petition at page 3).

Our longstanding interpretation is that the term "drug" in the patent listing provisions means the approved drug product. We successfully argued in *Pfizer* v. *FDA*, 753 F. Supp. 171 (D. Md. 1990), that the term "drug" as used in sections 505(b)(1) and 505(c)(2) of the act refers to the "drug product" for which the NDA was filed. Pfizer had maintained that "drug" meant both the drug substance (active ingredient) and the drug product, and thus any patent claiming any drug product which contained the active ingredient that was the subject of the approved NDA must be submitted, regardless of whether the patent claims the approved drug product itself. This case began with our refusal to list a patent in the Orange Book because Pfizer did not certify that the drug and the formulation or composition of the drug claimed by the patent were currently approved. The drug dosage form covered by Pfizer's approved NDA was a capsule, but the patent Pfizer had sought to list claimed a tablet.

The court upheld our position that: (1) An NDA approval covers a specific drug product; (2) the approved drug product becomes the listed drug; and (3) ANDA applicants must certify only to patents claiming that listed drug. The court found that "FDA's interpretation is not only reasonable but also consistent with the language of the statute, Congressional intent, prior judicial interpretations of [21 U.S.C.] § 355, and the agency's own regulations" (see 753

F. Supp. at 171–72). It also found that section 505(b)(1) of the act modifies the statutory definition of "drug" at section 201(g)(1) of the Act (21 U.S.C. 321(g)(1)) to allow listing only of patents which claim the drug "for which the applicant submitted the application." Further, the court noted that sections 505(b)(1)(B) and (C) of the act require that an NDA application contain "a full list of the articles used as components of such drug" and "a full statement of the composition of such drug," and that these requirements made sense only for a drug product and not for a drug substance that was independent of the approved NDA. Because Pfizer's NDA covered a specific drug product in capsule form (as opposed to covering the drug product's active ingredient alone or covering other dosage forms that contain the active ingredient), the court held that Pfizer could not list the patent covering the tablets.

In 1994, after the *Pfizer* decision had issued, we published a final rule that codified the patent listing requirement at 21 CFR 314.53 (see 59 FR 50338 (October 3, 1994)). Although the rule repeated the statutory requirement that the patent must claim the drug that is the subject of the NDA, the final rule replaced the proposed rule's reference to patents consisting of "drug (ingredient) patents" with patents consisting of "drug *substance* (ingredient) patents" (see 59 FR 50338 at 50343) (emphasis added). We also replaced "patents that claim a drug or drug product" with "patents that claim a drug *substance* or drug product" (*id.*) (emphasis added). Our intent was to clarify that the rule's reference to "drug" in the phrase "drug or drug product" was intended to mean "drug substance" rather than "drug product." (The rule mentioned drug products separately.) We made this change because some patents claim the approved drug product's active ingredient rather than the entire drug product (i.e., the drug product's active and inactive ingredients).

In other words, if the patent claims the drug substance that was approved in the NDA, it must be listed.

However, some courts interpreted § 314.53 differently than we had intended. In *Zenith Laboratories, Inc.* v. *Abbott Laboratories, Inc.*, 1996 WL 33344963 (D. N.J. 1996), Abbott had listed patents for the dihydrate form of terazosin hydrochloride (the drug substance in the NDA-approved product whose trade name was Hytrin) and also for the anhydrous form of terazosin hydrochloride that differed from Hytrin's drug substance only in its crystalline forms. (An anhydrous form of a chemical contains no water molecules, whereas a dihydrous form contains two water molecules.) Zenith had filed an ANDA to market a drug product containing a different form of terazosin hydrochloride, and claimed that the active ingredient in its product had a different crystalline structure from Hytrin, did not infringe the patent on Hytrin, and that Abbott's patents on the anhydrous form of the active ingredient did not cover the approved drug product. The court found that the patents at issue did claim the approved drug product. The court interpreted § 314.53(b) to mean that, if a patent claims the drug substance of an approved drug product, then the patent is covered by the approved drug product and may be listed in the Orange Book even if the patent claims a form of the drug substance that is different than the form in the approved drug product. Moreover, the court indicated that we may approve an ANDA for a drug product that contains the patented form of the active ingredient. The court also cited two statements from the Orange Book to support its ruling that different forms of the same active ingredient may be considered pharmaceutically equivalent if their dissolution, solubility, and absorption are the same as the listed drug. The court concluded that the patents were likely to be construed

as claiming the drug substance for the NDA-approved drug regardless of the differences in hydration.

In *Ben Venue Laboratories, Inc.* v. *Novartis Pharmaceutical Corp.*, 10 F. Supp.2d 446 (D.N.J. 1998), Novartis had listed a patent which claimed the crystalline pentahydrate form of Aredia (pamidronate disodium). The ANDA applicant argued that the appropriateness of the patent listing turned on whether Novartis' approved product contained a crystalline hydrate of pamidronate (*id.* at page 453). The parties did not dispute that the final drug product did not contain the pentahydrate form of pamidronate. Novartis admitted that its dosage form contained an anhydrous form of pamidronate, but argued that patent was properly submitted because the patent covered the "drug substance" and because § 314.53 required the listing of such patents (*id.*). The court found that it was proper to list a patent that claims a component of the approved drug product even when that component does not appear in the exact same form in the final drug product (*id.* at pages 453–457). The court distinguished the *Pfizer* opinion as depending largely on the applicant's attempt to list a patent for a new, unapproved tablet (*id.* at page 455).

The court also noted that *Pfizer* predated our 1994 final rule and stated that:

The statute governing listing of patents merely states that NDA applicants shall file "any patent which claims the drug." 21 U.S.C. § 355(b)(1). The regulations clearly indicate that the FDA interprets the ambiguous term "drug" in 21 U.S.C. § 355(b)(1) to include certain drug substances or active ingredient patents, and requires their listing in the Orange Book. The Court concludes that the FDA's construction of the statute to require listing of certain drug substance patents as well as drug product patents is a permissible reading of the statute, and the parties do not argue otherwise.

See *Chevron, U.S.A., Inc.* v. *Natural Resources Defense Counsel* [sic], 467 U.S. 837 (1984). Therefore Ben Venue's assertion that "the drug substance or active ingredient does not determine proper listing" and that "the drug product—and it alone—controls the proper listing,"* * * are inaccurate.

See 10 F. Supp.2d at page 455.

Although we were not a party to the litigation, we implicitly did not accept the conclusion or reasoning of the *Zenith Laboratories* and *Ben Venue Laboratories* decisions. On February 7, 2001, we wrote to Biovail Laboratories to confirm the propriety of a corrected patent listing under § 314.53(f). Biovail had changed its manufacturing process for Tiazac (diltiazem hydrochloride), but had not sought our approval before making those changes. The approved product contained diltiazem hydrochloride in time-release coated beads, whereas Biovail's changed product contained both immediate release diltiazem hydrochloride powder and time-release coated beads. Biovail asserted that the changes were within the scope of its approved NDA, yet we learned about the changes only through litigation between Biovail and another company. In our letter to Biovail, we stated that, "FDA does not list patents for drug substances, compositions, formulations and methods of use that are not approved for the listed drug" (see Letter from Ralph Lillie, Director, Office of Information Technology, Center for Drug Evaluation and Research, to Biovail Laboratories, Inc., dated March 23, 2001). We also took the position that Biovail had to submit a supplement to its NDA to cover the immediate release diltiazem component and stated that:

Patents for drug substances, composition, formulations, and methods of use that are not approved for the listed drug are not listed in the Orange Book. A patent

submitted in an application or supplement that is not yet approved will be listed in the Orange Book only if, and when the drug product is approved.

(See *id.* at page 2.)

On November 21, 2000, we responded to a citizen petition (FDA docket number 00P–0499) submitted by Lord, Bissell & Brook on behalf of Apotex, Inc. The petition asserted, in part, that two patents claiming anhydrous forms of paroxetine hydrochloride did not claim the hemihydrate listed drug. (An anhydrous form of paroxetine hydrochloride has no water molecules associated with it, whereas a hemihydrate form has one water molecule associated with every two paroxetine molecules.) Relying on the NDA holder's representations that the patents claimed the approved drug product, we concluded that the patents had been correctly submitted for listing. We stated that, "Patents must be listed if they claim the drug substance, or active ingredient, of an approved drug product, or if they claim a drug substance that is the component of such a product" (Response from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Hugh L. Moore et al., Lord, Bissell & Brook, dated November 21, 2000, at page 6 (footnote omitted)). In a footnote, we noted that our position was "fully consistent with *Pfizer*" because the *Pfizer* case "involved the question of the listing of patents for a drug in a dosage form other than the dosage form approved by FDA" (*id.* at page 6, note 18), whereas the paroxetine situation involved a patent which, according to the NDA holder, claimed the approved drug product. We further stated that we considered anhydrous and hemihydrous forms of drug substances to be pharmaceutical equivalents and to contain the same active ingredient (*id.* at page 6, note 16). We cited *Zenith Laboratories* and *Ben Venue Laboratories* for the proposition that courts, rather than FDA, would resolve whether the patent covered the

approved drug. Our letter did not take issue with the holdings of those courts (*id.* at page 5, note 13).

Recently, in *Andrx Pharmaceuticals, Inc.* v. *Biovail Corp.*, 276 F.3d 1368 (Fed. Cir. 2002), a case involving the patent listing correspondence with Biovail Laboratories described in a preceding paragraph, the court held that "the critical question is the relationship of the patent to the drug products and drug substances covered by the NDA" (*id.* at page 1376). The issue in the *Andrx Pharmaceuticals* case was Biovail's listing of a patent that claimed an extended release formulation of diltiazem that was different from the one we had approved. In a footnote, the Court of Appeals for the Federal Circuit cited our 1994 final rule and interpreted the final rule as changing our patent listing procedures (*id.* at page 1377, note 5). The court stated that our supposed change in position was a "more liberal construction" of the statute and led to more patents being listed in the Orange Book (*id.*).

3. *Which Patents Would the Proposal Require to Be Listed or Not Listed?*

Given these court decisions which are not entirely consistent with our policies, the FTC Report, the FTC Citizen Petition, and other documents questioning patent listing requirements, we decided to clarify our regulations to describe the types of patents that must and must not be listed. Consequently, proposed § 314.53(b) would state, in relevant part, that an applicant submitting an NDA, amending an NDA, or submitting a supplement to an NDA:

* * * 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, *product by process patents*, and method of use patents. Process patents, *patents claiming packaging, patents claiming metabolites*, and *patents claiming intermediates* are not covered by this section, and information on these patents may not be submitted to FDA. *For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application within the meaning of section 505(j)(2)(A)(ii) of the Act. For patents that claim a 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. 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 that are the subject of a pending or approved application. For approved applications, the applicant shall identify the indication or other condition of use in the approved labeling that corresponds to the listed patent and claim identified.*
* * *

We have italicized the new or revised regulatory language to make it more readily identifiable for this preamble discussion. We explain the proposed changes in more detail in the following paragraph.

a. *What Patents Must Not Be Listed Under the Proposal?*

Proposed § 314.53(a) would expressly state that information on patents claiming packaging, patents claiming metabolites, and patents claiming intermediates must not be submitted. In general, we find that these patents fail to meet the two prong criteria for listing because they do not claim the approved drug product.

Patents claiming a drug product's packaging or container may not be listed. We find that, although information regarding a drug's packaging or container

is part of an NDA (see 21 CFR 314.50(d)(1)(ii)(a)), we do not approve that packaging or container per se. The packaging or container is therefore distinct from the approved drug product, so a patent that claims a type of packaging or container fails to satisfy the first prong because the patent does not claim the drug. In addition, in contrast to the active ingredient, inactive ingredients, and conditions of use, the Hatch-Waxman amendments do not identify a listed drug's packaging or container as an element for us to review or consider in determining whether to approve an ANDA or 505(b)(2) application.

The failure to claim the approved product is especially apparent for patents claiming metabolites because those metabolites exist only *after* a person has taken the drug and his or her body has broken the drug down into the metabolite. While there have been no court decisions regarding the listing of patents claiming a metabolite, one court has examined whether a person can seek patent term restoration for a patent claiming a metabolite rather than the approved drug itself. In *Hoechst-Roussel Pharmaceuticals, Inc.* v. *Lehman*, 103 F.3d 756 (Fed. Cir. 1997), a court had to decide whether the Patent and Trademark Office correctly interpreted the patent term extension provisions at 35 U.S.C. 156. The patent term extension provisions were part of the Hatch-Waxman amendments (as Title II of the Hatch-Waxman amendments). The patent term extension provisions require that the patent for which an extended term is sought to "claim" the approved drug (see 35 U.S.C. 156(a) and 156(g)(1)(B) (discussing how a product must have been subject to a regulatory review period before its commercial marketing or use and defining the regulatory review period, in part, in terms of an NDA approval)). However, the patent in question claimed a metabolite rather than the approved drug itself. The court considered the meaning of the term "claim," and the term's

relationship to the concept of infringement, and concluded that a patent claiming a metabolite or the use of a metabolite does not claim the approved drug product. The court's reasoning and conclusion are equally applicable to patent listings. Therefore, we conclude that a patent claiming a metabolite does not claim an approved drug and does not meet the statutory requirements for listing in the Orange Book.

The proposal would also instruct applicants not to submit patent information if the patent claims an intermediate. Intermediates are materials that are produced during the steps of the processing of active pharmaceutical ingredient, but are not present in the final drug product themselves (see Food and Drug Administration, "Guidance for Industry: Q7A—Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (August 2001)). Under existing FDA regulations, intermediates are "in-process materials" rather than drug substances or even drug components (see 21 CFR 210.3(b)(9); 211.110). Thus, patents that claim intermediates do not claim the approved drug product and, for that reason, fail the first prong for listing.

We note that, as is currently the case, patents that claim methods of use that are not approved for the listed drug or are not the subject of a pending application may not be submitted.

b. *What Additional Patents Would the Proposal Require to be Listed?*

1. *Product by Process Patents*

The proposal would include "product by process patents" in the class of patents that must be listed because product by process patents are a type of product patent. In brief, a product by process patent claims a product by using or listing process steps to wholly or partially define the claimed product (see *In re Luck*, 476 F.2d 650 (C.C.P.A. 1973); *In re Brown*, 459 F.2d 531, 535

(C.C.P.A. 1972)). In a product by process patent, the claims must particularly point out and distinctly claim the product or genus of products for which patent protection is sought (see *In re Brown*, 459 F.2d at page 535). These patents, therefore, meet the two-prong criteria for patent listing because they claim the approved drug product and are of a type with respect to which a claim of patent infringement could reasonably be made if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug; consequently, including product by process patents in the class of patents that must be listed is appropriate.

We must emphasize that product by process patents differ from process patents because, in a product by process patent, the patented invention is the product (as opposed to the process used to make the product) (see *In re Bridgeford*, 357 F.2d 679, 682 (C.C.P.A. 1966)). Section 505(b)(1) of the act does not require information on process patents, and we do not list process patents in the Orange Book (see §§ 314.50(i)(2) and 314.53(b)).

We are concerned, however, that persons unfamiliar with patent law might confuse product by process patents with process patents, and seek to list process patents with us. Therefore, we invite comment on ways to ensure that only appropriate product by process patents are listed, while maintaining the act's restriction against listing process patents.

2. *Patents Claiming a Different Form of the Drug Substance*

Section 314.53(b) currently states, "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." The proposal would revise this sentence to read as follows:

For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application within the meaning of section 505(j)(2)(A)(ii) of the act. For patents that claim a 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.

This would mean that an applicant would be able to submit patent information on a drug substance even when the patented drug substance was a different form than the drug substance that is the subject of the pending or approved NDA as long as the drug substances are the "same" active ingredient under section 505(j)(2)(A)(ii) of the act. Whether two different drug substances are the "same" active ingredient is a scientific determination based upon the specific characteristics of the drug substances involved. We have, for example, determined that anhydrous and hydrated entities, and different polymorphs (different crystalline forms of the same substance), may be the "same" active ingredient (see Food and Drug Administration, "Approved Drug Products With Therapeutic Equivalence Evaluations," 22nd Ed., section 1.7 at page xv (2002)). Therefore, for example, if the approved drug substance was an anhyrdrate, and the patent claimed a hemihydrate, proposed § 314.53(b) would allow the applicant to submit patent information for the hemihydrate *if* the anhydrate and hemihydrate are the "same" active ingredient.

In making a determination that two drug substances are the same active ingredient, the NDA holder should consider whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability. We invite comment on whether we should revise the codified language to require the NDA holder to submit

additional information regarding the basis for the assertion that the drug substances are the same active ingredient.

We recognize that allowing NDA applicants and NDA holders to submit such patent information appears to conflict with our longstanding position that the patent must claim the approved drug product or the drug product that is the subject of the application. However, we believe this change in our patent listing policy is both reasonable and appropriate, and may even conserve agency and industry resources. Our rationale for allowing such drug substance patents to be listed depends, in large part, on our position concerning pharmaceutical and therapeutic equivalence. We consider drug products to be pharmaceutically equivalent if they have the same active ingredient(s), the same dosage form, the same route of administration, and are identical in strength or concentration. We consider drug products to be therapeutically equivalent if they are pharmaceutically equivalent and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. A major premise in the ANDA approval system is that the ANDA drug is therapeutically equivalent to the brand-name or "reference listed drug." In assessing whether the active ingredients in the reference listed drug and the generic drug product are the "same," and would support a determination of therapeutic equivalence, we have concluded that, in certain instances, the generic drug's active ingredient does not have to have the exact physical form as the reference listed drug's active ingredient (see Letter from Dennis Baker, Associate Commissioner for Regulatory Affairs, FDA, to Donald O. Beers and David C. Korn, Arnold & Porter, and to William J. McNichol, Jr., Marc J. Scheineson, and Tracy Zurzolo Frisch, Reed Smith LLP, dated February 15, 2002, at pages 3–4, 7, 9–11). We

have approved ANDAs when the drug substance in the generic drug product was a different polymorph than the drug substance in the listed drug. These products are therapeutically equivalent.

If a generic drug product can be the "same" as the reference listed drug, notwithstanding differences in the drug substances' physical form, then it is consistent to interpret "drug substance," for purposes of listing patent information, as including drug substances having different physical forms. We note that the Hatch-Waxman amendments contained the patent listing and ANDA provisions in the same title, so it would be logical for us to interpret these two provisions of the act in a consistent manner (see *Ben Venue Laboratories*, 10 F.Supp.2d, at page 457).

Additionally, it is conceivable that an ANDA applicant may file an ANDA for a drug product that contains a drug substance that does not share the same chemical structure as the NDA-approved drug, but is nevertheless covered by a patent. For example, assume that the NDA drug is a hydrated form of the drug substance, and the ANDA drug substance would be an anhydrate. If the patent for the NDA drug claims the hydrated drug substance, the ANDA applicant would be able to certify, correctly under current FDA regulations, that it was not infringing the patent and file a paragraph IV certification. However, if the patent owner also had a patent on the anhydrous form and the NDA holder were not allowed to submit patent information on the anhydrate because the patent does not claim the approved drug product, the ANDA applicant consulting the Orange Book would have no notice of the patent claiming the anhydrate. The missing patent information could mislead potential ANDA applicants into submitting ANDAs containing the anhydrate and unknowingly infringing the patent claiming the anhydrate. We, in turn,

could expend resources on reviewing an ANDA for a drug that is covered by the unlisted patent, and the patent owner could expend resources in defending the patent. This waste in agency and industry resources could be avoided if we require NDA applicants and NDA holders to submit information on patents that claim drug substances that are the same active ingredient as that in the listed drug product.

Again, we recognize that requiring the submission of patent information on drug substances that are the same active ingredient, even when those drug substances are in a form that differs from the drug substance in the approved drug product, appears to be a change from our previous position. As discussed previously, we believe this change is justified by our position on pharmaceutical and therapeutic equivalence. We invite comment as to the potential impact of this change on the submission of ANDAs and 505(b)(2) applications.

We also acknowledge that the interaction between the act's requirements, our pre-existing regulations, and our positions in court cases and elsewhere can make it difficult to interpret the act's patent listing requirements and ANDA and 505(b)(2) application approval requirements in a simple, harmonious manner. Although patents on different forms of an active ingredient are properly listed, and a pending ANDA containing a different form of the drug substance may be considered to have the "same" active ingredient as the reference listed drug, we must emphasize that this proposed rule does not alter the requirement for NDA holders to submit a supplement before changes are made to the synthesis of the drug substance (see 21 CFR 314.70(b)(1)(iv)). If an NDA holder wishes to use an active ingredient whose form is different from the active ingredient described in the approved NDA,

the NDA holder must seek our approval before it uses the different form of the active ingredient. Changes in the form of an active ingredient warrant the filing of a supplemental NDA because of the possible health consequences associated with the new form of the drug substance.

B. Proposed § 314.53(c)(2)(i)—What Does the Patent Declaration Say?

Section 314.53(c)(2)(i) requires a person submitting an NDA, an amendment to an NDA, or an NDA supplement, to submit a signed declaration as part of its submission of patent information if the patent covers the drug's formulation, composition, and/or method of use. The declaration states:

> 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*).

(Emphases in original.) We designed this declaration to help ensure that appropriate patents are listed and to preclude any need on our part to decide patent issues because we lack the patent expertise, resources, and statutory mandate to scrutinize patent listings (see 54 FR 28872 at 28909 (July 10, 1989)).

This declaration may be insufficient in practice to prevent NDA applicants and NDA holders from attempting to list inappropriate patents. The FTC Report suggested that "many of the later-issued patents do not appear to claim the approved drug product or an approved use of the drug" (see FTC Report at 37), but recognized that we lack the expertise and resources to review or decide patents disputes (*id.* at page 41; see also *aai Pharma* v. *Thompson*, 296 F.3d 227 (4th Cir. 2002) ("the FDA has no expertise in making patent law judgments")). The courts have also concurred in our view that we lack the authority to review the "listability" of patents (see *American Biosci.* v.

Thompson, 269 F.3d 1077, 1084 (D.C. Cir. 2001); *In re Buspirone Patent Litigation*, 185 F.Supp.2d 363, 371 (S.D.N.Y. 2002); *Watson Pharm., Inc.* v. *Henney*, Civ. No. U.S. Dist. LEXIS 2477, at 7–8 (D. Md. Jan. 17, 2001); *Mylan Pharm., Inc.* v. *Thompson*, 139 F.Supp.2d 1, 10–11 (D.D.C.) *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001)). The FTC Report also noted that ANDA applicants must certify to a listed patent even if they dispute the appropriateness of the listing (see FTC Report at 37; see also 21 CFR 314.94(a)(12)(vii)). Although we continue to lack the expertise, resources, and legal authority to examine patent issues, we can ask NDA applicants and NDA holders to provide more patent information to help ensure that only appropriate patents are listed. The proposed rule, if finalized, will prompt NDA holders and NDA applicants to make careful and well-considered representations in their patent declarations and produce greater compliance with our patent listing requirements.

The proposed rule would, therefore, revise § 314.53(c)(1) and (c)(2) by rewording the general patent declaration requirement in paragraph (c)(1) and by replacing the existing, general declaration at paragraph (c)(2)(i) with a more detailed declaration that would act as a "checklist" that would focus on patent claims and would ensure that applicants submit only appropriate patent information and stand behind the accuracy of that information. Proposed § 314.53(c)(1) and (c)(2)(i) would read as follows:

(1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the declaration described in paragraph (c)(2) of this section for each claim of the patent that meets the requirements described in paragraph (b) of this section.

(2) *Patent declaration.* For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), and/or method of use, the applicant shall submit the following declaration:

This is a submission of patent information for an NDA submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act).

Time sensitive patent information pursuant to 21 CFR 314.53 for NDA # _____

The following is provided in accordance with section 505(b) of the Act:

Trade Name: _____

Active Ingredient(s): _____

Strength(s): _____

Dosage Form(s): _____

Approval Date (if the submission is a supplement to an approved NDA): _____

Please provide the following information for each patent submitted, and identify the relevant claim(s) by number.

A. 1. United States patent number: _____

2. Expiration date: _____

3. Name of the Patent Owner: _____

4. Agent (if patent owner or applicant does not reside or have a place of business in the United States) _____

B. For each patent identified in A, please provide the following information:

1. The type of patent claims that apply to the drug substance or drug product that is the subject of the application:

2. Drug Substance (Active Ingredient)

___ Yes ___ No

a. Claim number(s): _____

3. Drug Product (Composition/Formulation):

___ Yes ___ No

a. Claim number(s): _____

4. Method of Use:

___ Yes ___ No

a. Claim number(s): _____

C. For each drug substance claim identified, please provide the following information:

1. Is the claim one that claims the drug substance that is the active ingredient in the approved or pending NDA, an amendment to the NDA, or a supplement to the NDA?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

2. Is the claim one that claims a drug substance that is the "same" active ingredient as the active ingredient in the pending or approved NDA, amendment to the NDA, or a supplement to the NDA?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

3. If the answer to question C.1 or C.2 is "yes," do you acknowledge that an ANDA or 505(b)(2) application containing the same active ingredient that is claimed by the patent is the "same" for ANDA or 505(b)(2) approval purposes?

___ Yes ___ No

[*If the answers to questions C.1, and C.2, or C.3 is "no," stop here. The patent may not be listed in the Orange Book as a patent that claims the drug substance.*]

D. For each drug product claim identified, please provide the following information:

1. Is the claim one that claims the approved formulation or composition and/ or the formulation or composition for which approval is being sought?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

[*If the answer to question D.1 is "no" in every instance, stop here. The patent may not be listed in the Orange Book as a patent that claims the drug product.*]

E. For each method of use claim identified, please provide the following information:

1. Is the claim one that claims:

(a) an approved method of use of the approved drug product? If "yes," please identify the use with reference to the approved labeling for the drug product and identify the relevant patent claim number(s);

___ Yes ___ No

(b) a method of use of the approved drug product for which use approval is being sought; or

___ Yes ___ No

(c) a method of use of the drug product for which approval is being sought?

___ Yes ___ No

If the answer to questions E.1(b) or (c) is "yes", please identify the use with reference to the proposed labeling for the drug product and identify relevant patent claim number(s).

[*If the answers to questions E.1(a) through (c) are "no," stop here. The patent may not be listed in the Orange Book as a patent that claims a method of use.*]

Note that the proposed declaration would emphasize identification of the relevant patent claims by number. The number would correspond to the patent

claim number in the patent itself. Precise identification of the relevant patent claims will help all parties focus on the same claim and may prevent arguments as to whether a particular claim pertained to the approved drug product or was infringed by the product described in an ANDA or 505(b)(2) application.

We are also proposing to require NDA holders and NDA applicants to identify the specific pending or approved use claimed by a method of use patent. This information will assist parties in assessing patent infringement matters and should expedite our approval of ANDAs and 505(b)(2) applications that do not seek approval for the protected use.

The proposal would also amend § 314.53(c)(2)(ii) to place more emphasis on patent claims rather than on the patent generally. Section 314.53(c)(2)(ii) currently instructs an NDA holder to amend its patent declaration within 30 days after approval of its application.

Current FDA regulations also address the content of the notice of certification of invalidity or noninfringement of patent that ANDA and 505(b)(2) application applicants must submit if their applications contain a paragraph IV certification (see §§ 314.95(c) and 314.52(c) respectively (21 CFR 314.95(c) and 314.53(c))). Section 505(j)(2)(A) of the act, however, states that we may "not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)." (No comparable statutory restriction exists for 505(b)(2) applications.) We invite comment on whether our current regulations regarding notice to the NDA holder and patent owner by ANDA applicants and 505(b)(2) application applicants could or should be amended.

C. *Proposed §§ 314.94(a) and 314.52(a)—How Many Times Can an Application's Approval Date Be Delayed for a 30-Month Period?*

We have consistently maintained that the Hatch-Waxman amendments create the opportunity for multiple 30-month stays to an ANDA's or 505(b)(2) application's approval date if those applicants submitted a paragraph IV certification and an action is brought for patent infringement within the statutory 45-day period. For example, assume that an ANDA applicant submitted a paragraph IV certification, provided the proper notice to the NDA holder and patent owner, and was sued for patent infringement within 45 days after providing the notice. Under section 505(j)(4)(B)(iii) of the act, we would be obliged to not approve the ANDA for a 30-month period beginning on the date of the receipt of the notice provided by the ANDA applicant to the NDA holder and patent owner, although the 30-month period could be longer or shorter depending on a court order or resolution of the litigation. If the NDA holder submitted new patent information to us, and the new patent information resulted in another paragraph IV certification and another action for patent infringement, our position has been that another 30-month stay in the effective date of ANDA approval could result.

We recently stated our position in *Andrx Pharmaceuticals, Inc.* v. *Biovail Corp.*, No. 01–6194-civ-Dimitrouleas/Johnson (S.D. Fla.). We argued that the 30-month stay provided by section 505(j)(5)(B)(iii) of the act "is not rendered inapplicable to a patent newly listed in the Orange Book simply because the holder of the NDA has already received the benefit of such a stay with respect to a previously listed patent for the same drug" (see Memorandum of Federal Defendants in Opposition to Plaintiff's Motion for Summary Judgment Declaring Additional 30-Month Stay Inapplicable or Eliminated, at page 5).

Andrx had argued that a 30-month stay in the approval date applies only where an ANDA applicant provides notice in the context of an original ANDA and not in an amended ANDA. We argued that section 505(j)(5)(B)(iii) of the act provides for a stay of up to 30 months regardless of whether the paragraph IV certification was part of an original ANDA or an amended ANDA. We stated that the act's reference to section 505(j)(2)(B)(i) of the act, which itself refers to sections 505(j)(2)(B)(ii) and (B)(iii) of the act, required that section 505(j)(2)(B) be read as a whole and, as a result, requires us to make a 30-month stay available whenever a paragraph IV certification was filed and timely patent litigation ensued, thereby permitting multiple 30-month stays of a single ANDA approval.

We also maintained, in *Andrx Pharmaceuticals, Inc.*, that if the 30-month stay applied only when an original ANDA contained a paragraph IV certification, an applicant could amend an ANDA to include a paragraph IV certification, and there would be no notice to the NDA holder or patent owner and no opportunity for even a single, 30-month stay. We stated that such a result could not be reconciled with the Hatch-Waxman amendments' intent to strike a balance between generic drug approval and encouraging future innovation (*id.* at page 9, note 6).

We note, along with the FTC Report, that the number of 30-month stays per product has been increasing. The FTC Report found that, before 1998, patent infringement litigation "generated, at most, one 30-month stay per drug product per ANDA," and most cases (eight out of nine) involved alleged infringement of one or two patents (see FTC Report at page 36). However, after 1998, FTC found that, for drug products with substantial annual net sales, patent litigation was increasing, with a growing number of NDA holders or

patent owners (five out of eight cases) alleging infringement of three or more patents (*id.*). The FTC Report even noted one instance where the NDA holder had listed 12 patents in the Orange Book (*id.* at page 45). The FTC Report also found that NDA holders were beginning to list later-issued patents, many of which "do not appear to claim the approved drug product or an approved use of the drug," after an ANDA had been filed, and this resulted in a delay of FDA approval by 4 to 40 months (*id.* at page 36). In some cases, a single ANDA has been subject to as many as five stays (*id.* at page 46). The FTC Report addressed multiple stays in the context of a limited number of "blockbuster" drugs. The total number of stays in ANDA approvals is higher, and we agree with FTC that the number of stays appears to be increasing over time.

Consequently, we examined the act to assess whether requiring successive 30-month stays was the only reasonable interpretation of the act. We determined that another reasonable interpretation existed. Accordingly, through this proposed rule, we intend to adopt a different interpretation of the act. Our revised interpretation would limit the number of 30-month stays to the opportunity for only one stay per ANDA. Our reasoning is as follows:

• Section 505(j)(2)(B)(iii) of the act states that if an ANDA is amended to "include" a paragraph IV certification, then the notice to the NDA holder and to the patent owner "shall be given when the amended application is submitted."

• However, if the ANDA contained a paragraph IV certification, then any ANDA amendment containing a paragraph IV certification does not amend the ANDA to "include" a paragraph IV certification because the ANDA already contained a paragraph IV certification.

• In the circumstances described previously, the submission of a second paragraph IV certification in an ANDA amendment or supplement does not trigger the notice requirement in section 505(j)(2)(B)(ii) of the act because the ANDA is never amended or supplemented to "include" (i.e., contain) a paragraph IV certification.

• Consequently, under section 505(j)(5)(B)(iii) of the act, only one 30-month stay in the ANDA's approval date is possible, because the subsequent paragraph IV certifications will not have resulted in a second notice to the patent owner and NDA holder, and the 45-day period for filing a patent infringement suit, as described in section 505(j)(5)(B)(iii) of the act, will not have run. To put it another way, if the ANDA applicant is not obliged to submit the notice to the patent owner and NDA holder, then the pre-requisites to trigger the 30-month stay in an ANDA's approval date are not met, so the 30-month stay would not be available.

A similar argument for a single, 30-month stay per application can be made for 505(b)(2) applications that contain a paragraph IV certification.

Under this interpretation of the act, ANDA and 505(b)(2) application applicants would still be required to make paragraph IV certifications where applicable, but the addition of a second paragraph IV certification to an ANDA or a 505(b)(2) application that had already contained at least one paragraph IV certification would not trigger an obligation to provide a second notice to the NDA holder or to the patent owner and would not result in another opportunity for a 30-month stay. Instead, as in the case of paragraph I (no patent information has been filed) or paragraph II (patent has expired) certifications, the subsequent paragraph IV certification would allow us to

approve the ANDA or 505(b)(2) application immediately if the Act would otherwise permit us to do so.

The parties would, of course, be free to litigate issues regarding patent infringement, but proposed multiple, 30-month stays per ANDA or 505(b)(2) application would no longer be possible. Our interpretation would not adversely affect a patent owner's ability to protect its patent rights. If an ANDA or 505(b)(2) application applicant makes one paragraph IV certification, the patent owner and the NDA holder would always receive notice and would always have the opportunity to protect the patented invention. If the NDA holder files *another* patent later, and the ANDA or 505(b)(2) application applicant believes that the later-filed patent is invalid or will not be infringed, the patent owner and NDA holder are still able to protect the later-filed patent because: (1) The notice already alerted the patent owner and NDA holder to the existence of the ANDA or 505(b)(2) application; and (2) any defense of the later-filed patent will not depend on the existence of a subsequent notice to the patent owner or NDA holder. In other words, with respect to later-filed or subsequently filed patents, the patent owner and NDA holder still have patent infringement and judicial remedies available to them even without receiving another notice. The patent owner, for example, can still seek an injunction to protect the patent on such terms as a court deems reasonable under 35 U.S.C. 283. If a court finds that the patent is infringed, the patent owner may be entitled to damages under 35 U.S.C. 284.

We recognize that there are other arguments to support a single, 30-month stay in each ANDA or 505(b)(2) application's approval date. For example, one argument could be that the act contemplates only one 30-month stay in an ANDA's approval date because section 505(j)(5)(B)(iii) of the act refers to "the"

30-month stay. This argument presumes that the original ANDA contained a paragraph IV certification and resulted in a 30-month stay. We do not concur with this interpretation of the act because, in certain situations, it could result in no notice to the patent owner or NDA holder. For example, if the original ANDA contained a paragraph III certification (stating that the patent will expire on a specific date), and the ANDA applicant later amends the ANDA to contain a paragraph IV certification, one could argue that no notice to the patent owner or NDA holder would be necessary, and there would not be an opportunity for even a single, 30-month stay. In contrast, under our proposed interpretation of the act, the opportunity for one 30-month stay in the abbreviated application's effective date always exists, and the patent owner and NDA holder would always receive one notice from the ANDA or 505(b)(2) application applicant who challenges at least one of the listed patents. This would preserve the balance between encouraging ANDA and 505(b)(2) application approvals and encouraging innovation because: (1) The elimination of multiple 30-month stays will lead to faster ANDA or 505(b)(2) application approvals, and (2) the patent owner and NDA holder will still receive notice and will be able to take steps to defend the patented invention from alleged patent infringement. As courts have observed, "The Hatch-Waxman Act represented Congress's efforts to strike a compromise between the competing interests of pioneer pharmaceutical companies and generic manufacturers" (see *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 139 F.Supp.2d 1, 4 (D.D.C. 2001); see also *Mylan Pharmaceuticals, Inc.* v. *Henney*, 94 F.Supp.2d 36, 52–53 (D.D.C. 2000) (interpretation of Hatch-Waxman must take into account the compromise nature of the statute); *Fisons Corp.* v. *Shalala*, 860 F.Supp. 859, 862 (D.D.C. 1994) ("A variety of federal courts have recognized that this Act

represents a compromise, and aids both sets of drug manufacturers; see, e.g., *Tri-Bio Laboratories* v. *United States*, 836 F.2d 136, 139 (3rd Cir. 1987))." A maximum of one 30-month stay per ANDA or 505(b)(2) application represents a reasonable compromise.

Additionally, we note that interpreting the act to allow only a maximum of one 30-month stay per ANDA or 505(b)(2) application is consistent with the specific legislative history that accompanied the passage of the Hatch-Waxman amendments.[1] When the 97th Congress considered patent term extension legislation, many members were concerned that the bill would not prevent brand-name companies from obtaining multiple patent term extensions for patents that claimed a drug and, by doing so, inhibit competition from generic drugs (see 128 Cong. Rec. H6916, H6919 (September 13, 1982) (remarks of Rep. Kastenmeier)). Some charged that the bill would extend the effective patent life of top-selling drugs for more than 17 years (the patent term that existed at the time) through "pyramiding" or "evergreening" of patents (*id.* at page H6922) (remarks of Rep. Gore). The House of Representatives, by a vote of 250 to 132, rejected passing the bill by suspension of the rules, and so the bill failed to be passed despite unanimous support in the Senate and strong support in the House. When the Senate revisited the legislation in the next year, the President of the Pharmaceutical Manufacturers Association (now known as the Pharmaceutical Research and Manufacturers of America) testified that, in 1982:

* * * critics of the bill sought to create the impression that innovative firms were acquiring patents in constellation, pyramiding one on top of another to extend

[1] We further note that, although reliance on legislative history may have its perils, its use is more justified where, as in this case, the statute is ambiguous (see, e.g., *PanAmSat Corp.* v. *FCC*, 198 F.3d 890, 895 (D.C. Cir. 1999) (stating that a court does not resort to legislative history "to cloud a statutory text that is clear") (citation omitted).

effective protection. Among people not knowledgeable about the intricacies of patent law, this understandably occasioned alarm and suspicion.

(See Hearing on S. 1306, Senate Judiciary Cmte., 98th Cong., 1st Sess. 56–57 (testimony of Lewis A. Engman, President, Pharmaceutical Manufacturers Association)).

The statutory language creating paragraph IV certifications, provisions for giving notice of such certifications, and rules governing amended applications is identical to language in S. 2748 as introduced by Senator Hatch in 1984. The House Judiciary Committee reported essentially identical language by voice vote, and the only relevant report language states that notice is required under paragraph 505(j)(2)(B)(iii) when an ANDA "is subsequently amended so as to bring it *within* this notice requirement" (see H. Rep. 98–857, Part 2, 98th Cong., 2d Sess. 14 (1984) (emphases added)). This understanding by the House Judiciary Committee suggests that if an ANDA applicant had provided notice to the patent owner and NDA holder, and then amended the ANDA to make a patent certification regarding a newly-filed patent, then the ANDA applicant would not have to provide another notice because, by virtue of its first notice to the patent owner and NDA holder, the ANDA applicant was *already* within the notice requirement. Our proposed interpretation is thus consistent with the legislative history.

For all these reasons, we propose to amend §§ 314.95(a)(3) and 314.52(a)(3) to state that the requirement to provide a notice of invalidity or noninfringement of patent:

* * * does not apply to a use patent that claims no uses for which the applicant is seeking approval. This paragraph also does not apply if the applicant amends its application to add a certification under [§ 314.94(a)(12)(i)(A)(*4*) for an ANDA

applicants or § 314.50(i)(1)(i)(A)(*4*) for 505(b)(2) application applicants] when the application already contained a certification under [§ 314.94(a)(12)(i)(A)(*4*) or § 314.50(i)(1)(i)(A)(*4*)] to another patent.

The proposed amendments to §§ 314.95(a)(3) and 314.52(a)(3), if made final, will lead to a changed interpretation of §§ 314.95(d) and 314.52(d) respectively. Sections 314.95(d) and 314.52(d) state that if an application is amended to include a paragraph IV certification, then the ANDA or 505(b)(2) application applicant shall send the notice of certification of invalidity or noninfringement of patent at the same time that it submits its amendment to us. Under the proposed rule, an ANDA or 505(b)(2) applicant who is amending its application to include a paragraph IV certification must provide notice to the patent owner and NDA holder only if the ANDA or 505(b)(2) application did not previously contain a paragraph IV certification.

III. Implementation

A. How Would the Rule Affect Notices?

Under the framework proposed in this rule, the possibility exists that if two ANDA applicants file paragraph IV certifications to a later-filed patent, and one ANDA applicant has already submitted a paragraph IV certification to a previously-filed patent, one ANDA applicant could be subject to a 30-month stay with respect to the later-filed patent while the other would not. To illustrate this problem:

1. Assume that ANDA applicant #1 files a paragraph IV certification to a patent, while ANDA applicant #2 files a paragraph III certification to the same patent. The patent owner brings a suit for patent infringement against ANDA applicant #1 and obtains a 30-month stay in the ANDA's approval date.

2. Assume that the NDA holder files another patent.

3. If ANDA applicants ## 1 and 2 both file paragraph IV certifications for the second patent, the proposed rule, if finalized, would not require ANDA applicant #1 to provide notice to the patent owner and NDA holder, because the ANDA previously contained a paragraph IV certification. However, ANDA applicant #2 is subject to a potential 30-month stay in the ANDA approval date because it would be required to provide notice to the patent owner and NDA holder.

While this hypothetical situation appears to treat the two ANDA applicants differently, we believe that our interpretation does treat the ANDA applicants alike, because both ANDA applicants would be subject to the possibility of only one 30-month stay in the ANDA approval date.

Our proposed interpretation of the 30-month stay does not affect an ANDA applicant's eligibility for 180-day exclusivity. In brief, section 505(j)(5)(B)(iv) of the act gives the ANDA applicant who files the first paragraph IV certification for a listed patent 180 days of exclusivity (against other ANDA applicants). We interpret the 180-day exclusivity provision as providing 180-day exclusivity to the first ANDA applicant whose ANDA contains a paragraph IV certification to a patent, even if the paragraph IV certification is one that would not result in an obligation to notify the patent owner and NDA holder and would not subject the applicant to the risk of patent litigation and a 30-month stay. The FTC Report suggested that if only a single, 30-month stay per ANDA were allowed, the number of patents listed after NDA approval might decrease (see FTC Report at page v).

B. How Would the Rule Affect Pending Applications?

Assuming that we issue a final rule, we intend to apply the rule to pending applications as follows:

• For patents filed for an NDA that has not been approved by the effective date of a final rule, the rule would apply on the effective date. For example, if the final rule were to become effective 60 days after the date of publication in the **Federal Register**, and an NDA was pending on the 60th day after the final rule's publication date, the NDA applicant would have to comply with the final rule's patent listing and patent declaration requirements. ANDA and 505(b)(2) application applicants would be subject to the revised notice requirement. Each ANDA or 505(b)(2) application referencing that NDA would be subject to the possibility of only one 30-month stay per ANDA or 505(b)(2) application.

• If we have approved the NDA as of the final rule's effective date, and no ANDA has been filed before that date, then any patent listed before that date would be subject to the pre-existing regulation. For example, if the final rule were to become effective 60 days after the date of publication in the **Federal Register**, and we approved the NDA on the 59th day after the date of publication, the NDA applicant would *not* have to amend its patent listing and patent declaration to comply to the final rule. ANDA and 505(b)(2) applications submitted after the effective date would be subject to the revised notice requirement. Each ANDA or 505(b)(2) application referencing that NDA would be subject to the possibility of only one 30-month stay per ANDA or 505(b)(2) application.

• If we have approved the NDA as of the final rule's effective date, and an ANDA or 505(b)(2) application has been filed before that date, then any patent listed before that date would be subject to the pre-existing regulation, as described in the example immediately above. The ANDA or 505(b)(2) application applicant would have to provide notice to the patent owner and

NDA holder if the ANDA or 505(b)(2) application contained a paragraph IV certification. Multiple 30-month stays in the approval date would be possible.

• If the NDA holder or NDA applicant files patent information after the final rule's effective date, then the NDA holder or applicant is subject to the final rule's patent listing and patent declaration requirements, and ANDA or 505(b)(2) application applicants would not have to provide notice if their applications previously contained a paragraph IV certification. Only one 30-month stay per each ANDA's or 505(b)(2) application's approval date would be possible. Multiple 30-month stays in the approval date would be possible.

This proposed rule provides sufficient notice to all interested parties, whether they are NDA holders, NDA applicants, ANDA applicants, or 505(b)(2) application applicants, to adjust their submissions and actions by the time we issue a final rule. (This assumes, of course, that we issue a final rule.) NDA holders who wish to receive the benefits of the pre-existing regulation will have enough time to decide whether to pursue additional patents and to list them. ANDA and 505(b)(2) application applicants will be able to plan their submissions more efficiently as they will know whether their applications will be subject to the possibility of one or more 30-month stays of approval if they make a paragraph IV certification. If we were to adopt an alternative implementation plan, we would risk upsetting legitimate expectations held by those who had relied on our earlier interpretation of the act. However, we invite comments on how a final rule should be implemented.

IV. Legal Authority

Our principal legal authority for the proposed rule exists at sections 505 and 701 (21 U.S.C. 371) of the act. Section 505(b) of the act describes the contents of an NDA and 505(b)(2) applications, including the patent listing and

patent certification requirements. Section 505(j) of the act describes the contents of an ANDA, including patent certification requirements. Both sections 505(b) and 505(j) of the act also describe the 30-month stay of approval dates of a 505(b)(2) application or ANDA if the 505(b)(2) applicant or ANDA applicant made a paragraph IV certification and a timely action for patent infringement ensues.

The proposed rule would clarify the types of patents which NDA applicants and NDA sponsors must and must not submit to FDA for listing in the Orange Book. It would also require a more detailed patent declaration from NDA applicants and NDA holders.

For 505(b)(2) applicants and ANDA applicants, the proposal would have the effect of reducing the number of notifications sent to patent owners and NDA holders. Sections 505(b)(2)(A) and 505(j)(2)(A)(vii) of the act, respectively, require patent certifications, while sections 505(b)(3)(A) and 505(j)(2)(B) of the act require those applicants who have made a paragraph IV certification to provide a notice to the patent owner and NDA holder. Because the proposal would not require ANDA applicants and 505(b)(2) applicants to provide notice if: (a) the original ANDA or 505(b)(2) application contained a paragraph IV certification; and (b) the applicants amend their applications to include another paragraph IV certification in response to another patent listing, fewer notifications of invalidity or noninfringement of a patent would result.

Thus, section 505 of the act, in conjunction with our general rulemaking authority in section 701(a) of the act, serves as our principal legal authority for this proposal.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) and 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Executive Order 13132: Federalism

The agency has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). We describe these provisions below in this section of the document with an estimate of the annual reporting burden. Our estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

We invite comments on: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed

Description: The proposed rule would clarify the types of patent information that must and must not be submitted to FDA as part of an NDA or as an amendment or supplement to an NDA. The proposal would also require persons submitting an NDA or amendment or supplement to such an application to make a detailed patent declaration as part of the application. The proposal would also permit the possibility of only one 30-month stay of each ANDA's or 505(b)(2) application's approval date in the event of patent infringement litigation because the proposal would not require ANDA applicants or 505(b)(2) applicants to provide a notice of certification of invalidity or noninfringement of patent if their applications already contain such a certification.

Description of Respondents: Persons submitting, amending, or submitting a supplement to an NDA, and persons submitting an ANDA or 505(b)(2)

application containing a patent certification of invalidity or noninfringement of patent.

We estimate the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No of Respondents	Frequency of Responses	Total Annual Responses	Hours per Response	Total Hours
314 50(a) through (f), (h), and (k)	80	1 55	124	1,690	209,560
314.52(a)(3) and 314 95(a)(3)	37	1	37	16	592
Total					210,152

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Our estimates are based on the following assumptions.

• According to our earlier information collection estimates for §§ 314.52 and 314.95, there are an estimated 37 respondents who provide a notice of certification of invalidity or noninfringement of patent each year, and each respondent submits an estimated 2 responses, with an estimated 16 burden hours per response. Because the proposed rule would allow only one 30-month stay in the effective date of approval for each 505(b)(2) application or ANDA, this would mean that these 505(b)(2) or ANDA applicants would (if the rule is finalized) file only one notice per year (unless they are filing multiple applications for different drugs and making paragraph IV certifications in more than one case). So, assuming that these applicants submit only one 505(b)(2) application or ANDA per year that contains a paragraph IV certification, the applicants would submit only one notice of certification of invalidity or noninfringement of patent each year. Thus, the information collection burden for §§ 314.52 and 314.95 would decrease to 592 hours (37 respondents x 1 response per respondent x 16 hours per response = 592 hours).

• To estimate the number of enhanced patent declarations that will be submitted annually, we referred to historical data on submissions of NDAs. In 2001 and 2002, we received 94 and 66 NDAs respectively. We therefore estimate that there will be 80 ((94 applications + 66 applications) / 2 years

= 80 applications/year) annual instances where an NDA applicant or NDA holder would be affected by the proposed patent listing and patent declaration requirements. According to our earlier information collection estimates for § 314.50(h) (the provision under which we covered patent listing and patent declaration matters as described in § 314.53), there are an estimated 1.55 annual responses per respondent. So, using the same 1.55 ratio, this would mean that 80 NDA applicants and NDA holders would submit 124 annual responses (80 respondents x 1.55 responses per respondent = 124 responses). However, proposed § 314.53(b) and (c) would have different impacts on the hours per response. On the one hand, proposed § 314.53(b) might decrease the reporting burden because it would specify certain patents that must not be filed in the Orange Book and thus discourage NDA applicants and NDA holders from submitting information on those patents. On the other hand, proposed § 314.53(b) would also require NDA applicants and NDA holders to submit patent information on different forms of the drug substance, and this could result in more patent information being submitted. We cannot determine whether the potential net effect will increase, decrease, or not change the overall burden associated with submitting patent information, so we have not assigned any change in the total reporting burden for the proposed change in patent information alone. In contrast, proposed § 314.53(c) would make the patent declaration more detailed. The change in the declaration would increase the burden hours per response in § 314.50(h) (the provision under which we covered patent declarations described in § 314.53(c)) because respondents would be required to be more precise in their declarations. Based on other rules that require respondents to compile and submit information in their possession, we estimated that the revised patent declaration will result in an

additional information collection burden of 24 hours. However, the previous burden hour estimate of 1,666 hours for § 314.50 covered paragraphs (a) through (f), in addition to paragraphs (h) and (k). We are unable to determine how many of the 1,666 hours were devoted to patent declarations, so, in this table, we simply add 24 hours to the 1,666 hour estimate for § 314.50(a) through (f), (h), and (k), resulting in a burden hour estimate of 1,690 hours (1,666 hours + 24 hours) to account for a respondent's need for more time to make and verify the patent declaration. Thus, the information collection burden for § 314.50(a) through (f), (h), and (k) would increase to 209,560 hours (124 annual responses x 1,690 hours per response = 209,560 hours). We invite comment as to whether we need to adjust our estimate of 24 burden hours per response.

We have submitted the information collection requirements of this rule to OMB for review. Interested persons are requested to send comments regarding information collection to the Office of Information and Regulatory Affairs, OMB (see **ADDRESSES**).

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, and the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages, distributive impacts, and equity). Unless the agency certifies that the rule is not expected to have a significant economic impact on a substantial number of small

entities, the Regulatory Flexibility Act, as amended by SBREFA, requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. Section 202 of UMRA requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation). We have conducted analyses of the proposed rule, and have determined that the proposed rule is consistent with the principles set forth in the Executive order and in these statutes.

The proposed rule is an economically significant regulatory action as defined by the Executive order. With respect to the Regulatory Flexibility Act, the agency certifies that this proposed rule is not expected to have a significant impact on a substantial number of small entities. The proposed rule is also a major rule under the Congressional Review Act. The discussion of costs and benefits is consistent with the requirements of the Unfunded Mandates Reform Act.

A. Objectives of the Proposed Regulation

The proposed rule has multiple objectives. We are clarifying the types of patents that must and must not be listed and revising the declaration that NDA applicants must provide regarding their patents. In addition, through this proposal, we are adopting a different interpretation of the act that will limit the number of 30-month stays to one per ANDA or 505(b)(2) application. This clarification, revision, and reinterpretation will help ensure that NDA applicants list appropriate patents in the Orange Book while preventing the NDA holders from thwarting generic entry through the use of multiple 30-

month stays. Through these actions, we are preserving the balance struck in the Hatch-Waxman Amendments between encouraging innovation and encouraging the availability of generic drugs. The estimated 10-year total costs of this proposed rule are approximately $51.5 billion and the annualized cost is $4.9 billion. The estimated 10-year total benefits of this proposed rule are approximately $53.9 billion and the annualized benefit is $5.1 billion. These 10-year total benefits include consumer savings of approximately $34.8 billion from earlier access to less expensive prescription pharmaceuticals. The 10-year benefits exceed the costs by approximately $2.4 billion and the annualized benefits exceed the annualized costs by approximately $230 million.

1. The 30-Month Stay

The Hatch-Waxman Amendments benefit consumers by bringing lower priced generic versions of previously approved drugs to market, while simultaneously promoting new drug innovation through the restoration of patent life lost during regulatory proceedings. A firm wishing to market a generic version of a previously approved innovator drug can submit an ANDA. An ANDA refers to a previously approved NDA (the "listed drug") and relies upon our finding of safety and effectiveness for the listed drug.

Persons submitting an ANDA or a 505(b)(2) application must make certifications regarding the listed patents claiming the drug they wish to duplicate. The applicant must certify one of the following for each patent: (1) That no patent information on the drug product that is the subject of the ANDA has been submitted to us; (2) that such patent has expired; (3) the date on which such patent expires; or (4) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the

ANDA is submitted. These certifications are known as "paragraph I," "paragraph II," "paragraph III," and "paragraph IV" certifications, respectively.

A paragraph IV certification begins a process in which the question of whether the listed patent is valid or will be infringed by the proposed generic product may be answered by the courts prior to the expiration of the patent. The ANDA or 505(b)(2) application applicant who files a paragraph IV certification to a listed patent must notify the patent owner and the NDA holder for the listed drug that it has filed an application containing a paragraph IV certification. The notice must include a detailed statement of the factual and legal basis for the applicant's opinion that the patent is not valid or will not be infringed. If the NDA holder or patent owner files a patent infringement suit against the ANDA or 505(b)(2) application applicant within 45 days of the receipt of notice, we may not give final approval to the ANDA or 505(b)(2) application for at least 30 months from the date of the notice. This 30-month stay per ANDA or 505(b)(2) application will apply unless the court reaches a decision earlier in the patent infringement case or otherwise orders a longer or shorter period for the stay.

We recognize that, in recent years, NDA holders have been able to use multiple 30-month stays to delay generic competition. Under current regulations, the patent certification process allows for one or more 30-month stays of an ANDA or 505(b)(2) application's approval. NDA holders can prevent FDA approval of ANDAs or 505(b)(2) applications beyond the initial 30-month stay by listing an additional patent in the Orange Book after the applicant has filed its ANDA or 505(b)(2) application. These applicants would be required to re-certify to the newly-listed patent. The NDA holder would then be given 45 days to file suit for patent infringement, and our approval of the initial

ANDA or 505(b)(2) application would be delayed for an additional 30-month period from the notice date or until a court decision in the newly instituted patent litigation.

According to the FTC Report, from 1992 to 2000, NDA holders have listed patents in the Orange Book after an ANDA has been filed for a drug product on eight occasions. Six of these eight occasions have occurred since 1998. In all eight of these instances, the subsequent patent resulted in a delay to generic access to markets beyond the initial 30-month stay. We are not aware of any case in which a court has decided that the ANDA infringed upon the subsequent listed patent. According to the FTC Report, in the four instances of multiple stays in which a court has decided on the validity or infringement of a later-listed patent, the patent has been found either invalid or not infringed by the ANDA.[2]

2. The Economic Impact of Generic Competition

The generic drug industry plays an important role in the economics of the healthcare industry. According to Caves, Whinston, and Hurwitz (1991), generic drug prices can be as little as 20 percent of the brand-name price for the same product.[3] Laws encouraging doctors to prescribe generic drugs when available are a part of the current effort to hold down the cost of healthcare.[4] A report from the Congressional Budget Office (CBO) report estimated that in 1994 (when the generic drug market was smaller than its current size) consumers saved between $8 and $10 billion by substituting generic for brand-

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[2] FTC Report, p. iv.

[3] Caves, Richard, M. D. Whinston, and M. A. Hurwitz, 1991. "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," Brookings Papers in Economic Activity: Microeconomics, p. 36.

[4] Hellerstein, Judith K. 1994. "The Importance of the Physician in the Generic Versus Trade-Name Prescription Decision," *RAND Journal of Economics*: 29:1:108–136.

name drugs in pharmacy sales.[5] While the first 30-month stay enhances the incentive to innovate, subsequent stays generated by later-listed patents do not seem to give rise to the same incentives in most cases. By using multiple 30-month stays, NDA holders are able to delay competition from generic drugs. Delaying generic competition harms consumers by slowing the introduction of lower priced products to the market and thwarts the intent of the Hatch-Waxman Amendments.

The agency considered potential impacts on innovation and believes any negative effect to be minimal. While the initial 30-month stay is part of the balance struck in the Hatch-Waxman amendments to reward innovation, the subsequent stays are not part of this balance. The patents that form the basis for these subsequent stays do not appear to warrant automatic protection from generic competition.

According to the FTC report, every court ruling involving a subsequent 30-month stay has found the underlying patent to be either invalid or not infringed. Also according to the FTC report, extending patents through multiple stays is a strategy that has become popular in the last few years and is not a longstanding universally-recognized source of research funding. Subsequent stays could actually hinder innovation through the replacement effect, in that they provide a disincentive for an NDA holder to improve upon its own product. Moreover, to the extent that subsequent 30-month stays might

[5] Congressional Budget Office, *How Increased Competition From Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998). Note that the sale of drugs through pharmacies is a subset of all drug sales so total savings to consumers would be expected to be higher than the given figure.

be associated with increases in spending on research, these increases do not necessarily improve social welfare.[6]

B. Costs of the Regulation

This section develops estimates of the cost to NDA holders from the proposed rule. As previously stated, this proposed rule clarifies those types of patents that must or must not be listed and eliminates the use of multiple 30-month stays per ANDA to delay generic competition. The innovator drug industry, as NDA holders, would be expected to bear the costs of the proposed rule. Generic drug companies and consumers would be expected to benefit. The impact on these entities that benefit is addressed in section III.C of this preamble. We do not estimate a specific impact involving those submitting 505(b)(2) applications. We recognize these applicants, like those submitting ANDAs, must make certifications and would be affected by this proposed rule. We believe any benefits would be difficult to quantify with any precision and would be quite small, relative to the benefits to generic drug companies.

This proposed rule will be costly to NDA holders because earlier generic competition will erode innovator market share. This loss of market share to generics will result in reduced revenues to the innovator. These reduced revenues would be mitigated somewhat by a reduction in the administrative, marketing, and sales expenses.

To estimate the impact of earlier generic competition, we estimate the revenues to NDA holders and generics under a base case scenario under which multiple 30-month stays per ANDA are not allowed and a scenario in which

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[6] A more detailed discussion of the replacement effect and of the relationship between research and social welfare can be found in Jean Tirole, *The Theory of Industrial Organization* (Cambridge: MIT Press, 1988), pp. 392, 399–400.

generic entry may be delayed subject to an additional stay. The impact of the proposed rule would be the difference between the two scenarios.

1. Delaying Generic Competition

To estimate the impact of delays to generic competition, we use a modified version of the economic model from our report to Congress on the pediatric exclusivity provision to the Food and Drug Administration Modernization Act.[7] Generic entry erodes the listed drug's market share, typically over a period of several years. At the same time, the price of the typical generic drug is also falling. By tracking the decline of listed drug's market share and the fall in the price of the generic competition, the model calculates changes in sales over time for innovator and generic sectors.

In the model, we assume the reference listed drug's market share falls from 100 percent to 60 percent in the first year of generic marketing, and then to 45 and 30 percent in years two and three. The price of the average generic drug falls with time, and this is also captured by the model. The model assumes for each 6-month interval over the first 3 years of competition, the generic price as a fraction of innovator price falls from 100 percent at introduction, to 80 percent after 6 months, and finally 33.5 percent after 3 years.[8] Several studies have shown generic competition to have only very small effect on innovators' prices.[9] Innovator prices do frequently rise after generic entry, but we lack the data to confidently incorporate an estimate of this into this model. If innovator price increases were incorporated into this model, the

[7] U.S. Food and Drug Administration, *The Pediatric Exclusivity Provision: Status Report to Congress*, January 2001, p. 43

[8] The decline over 3 years at 6-month intervals is as follows: 100 percent at introduction (0 months); 80 percent (6 months); 60 percent (12 months); 52.5 percent (18 months); 45 percent (24 months); 37.5 percent (30 months); 33.5 percent (36 months). The ultimate price ratio of 33.5 percent is consistent with a market with 10 generic entrants, per Caves, Whinston, and Hurwitz (1991), p. 36, table 9.

[9] See Box 4 in Congressional Budget Office (1998), p. 30.

magnitudes of the estimated impacts would be expected to be larger. We request comment providing data on price behavior after generic entry into the market.

The model calculates the impact on innovator and generic sectors each month for a 10-year period. Using immediate generic entry as a base case, the model calculates the relative impact of delaying entry for a certain number of months. These monthly impacts on each sector are converted to present value using a 7 percent discount rate.

According to appendix H of the FTC report, there have been 8 multiple 30-month stays, but the frequency of these stays has been increasing. Four drugs experienced multiple stays during 2000 and 2001. Based on this information, we assume that, absent this proposed rule, there would be 2 (4 drugs/2 years) situations with multiple 30-month stays each year. Thus, in calculating the annual impact of this proposed rule, we multiply the peak annual sales of the average affected drug by 2 to account for the frequency of the event. While we believe this to be a reasonable estimate, we recognize, as mentioned in the FTC Report, that a substantial sales volume of brand-name drug products will be coming off patent in the next few years. If there are more drugs affected by this rule than we estimate, this would increase both the benefits and costs of this rule.

To develop a profile of the typical drug for which there were multiple 30-month delays, we started with the instances in Appendix H and table 4–3 of the FTC Report. As two instances from the FTC report concern different dosage forms of the same drug, gabapentin, we count it only once in our analysis. Generic competition for one of the drugs, Cisplatin, was delayed because of a single 30-month stay and an alleged double patent. As we do

not believe this situation is addressed by this proposed rule, we eliminated it from the analysis. The information on the six remaining drugs is contained in table 2.

TABLE 2.—DRUGS USED IN ANALYSIS

Active Ingredient	FTC Stay Period (Months)	Estimated Additional Stay Period (Months)	Estimated Peak Sales (000)
Buspirone	30[1]	4	$700
Terazosin	70[2]	46	$580
Gabapentin	37	24	$1,710
Paroxetine	65	34	$3,780
Paclitaxel	60[1]	3	$1,020
Diltiazem	60[1]	28	$380
Average	50 (+20)	+23	$1,360

[1] Potentially, but actually shorter because of a court decision.
[2] Periods not overlapping.
Sales Data Sources: Buspirone 2000 data, BMS Web site; Terazosin 1999 data, Pharmacy Times Web site; Gabapentin 2001 data, Drug Topics Web site; Paroxetine 2001 data, Scrip 2737, p. 15; Paclitaxel 2000 data, BMS Web site; Diltiazem 2001 data, Forest Form 10K. For data prior to 2001, sales were escalated to the 2001 level using CPI-U. For drugs that have not yet reached peak sales, the peak was estimated with a linear projection.

Table 2 includes the inflation adjusted peak sales and subsequent delay for each of the six drugs. As a reference, we include delay information from the FTC report. Based on the delay and sales information for the six drugs, we find the typical delayed drug to have peak annual sales of $1,360 million and subject to a 23-month delay. As we do not possess current sales figures for all the drugs involved, we invite comment on the accuracy of these estimates.

2. Impact of Delay on the Innovator Sector

The model results obtained from comparing the no delay and delay scenarios are provided in table 3. To account for the frequency of occurrence, we multiply the peak sales estimate by 2. To the extent that this proposed rule would eliminate multiple 30-month stays per ANDA after the first, the estimated impact on innovators would be an annual revenue decrease of $3,159.50 million (approximately $3.2 billion).

TABLE 3.—RESULTS OF DELAY ANALYSES

Scenario	Sales (000)	Delay (Months)	Impact (In Millions)		
			Innovator	Generic	Consumer
Base Case	$2,720[1]	23	($3,160)	$1,120	$2,040

[1] Includes 2 0 frequency factor

The cost impact on innovators is driven by the fact that a delay in generic entry extends the time the innovator collects peak sales and shortens the time the innovator collects 30 percent of peak sales. Absent discounting, the impact on innovators would be the length of the delay times 70 percent of the peak innovator drug revenues.

This impact on innovators may be mitigated to a small degree by potential decreases in the administrative, marketing, and sales costs associated with the product. A recent study of top pharmaceutical companies found that marketing, administrative, and advertising expenses averaged 27 percent of revenues.[10] Part of this figure includes certain fixed costs that would not change with a decline in revenues. Moreover, to the extent that some of these support costs are discretionary, they would most likely be focused on periods of intense marketing, such as product roll-outs. Nevertheless, with the erosion of market share, the rewards to marketing would decline and the need for administrative support would be expected to decrease.

Assuming half the 27 percent figure to be discretionary support costs, and the discretionary support costs for the product in question to be one-third of the average, then discretionary support costs would be 4.5 percent of revenues (27 percent/6). The relevant annual cost reduction would be $142.2 million ($3.160 billion x 4.5 percent). As we lack precise data on the relationship between revenues and support costs, we invite comment on the accuracy of this estimate.

[10] Families USA, *Profiting From Pain: Where Prescription Dollars Go*, July 2002, p. 3.

3. Other Issues Related to Burdens to Innovators

The proposed rule would require NDA holders to submit a more detailed patent declaration. To estimate the number of enhanced patent declarations that will be submitted annually, we referred to historical data on submission of NDAs, excluding those for orphan drugs. In 2000 and 2002, there were 94 and 66 NDAs respectively. We therefore estimate that there will be 80 ((94 + 66) / 2) annual instances where an NDA holder or NDA applicant will face this additional declaration burden. Based on earlier information collection estimates, we assume there to be an estimated 1.55 annual responses per respondent. Using this same 1.55 ratio, this would mean that the 80 NDA applicants and NDA holders would submit 124 annual responses (80 respondents x 1.55 responses per respondent).

We believe that, while the NDA holder or NDA applicant possesses the additional patent information, there will be a burden in completing the more detailed declaration. Based on other rules that require respondents to compile and submit information in their possession, we estimate the burden to be 24 hours per event. A regulatory affairs specialist could perform the tasks associated with this process. Based on the total average hourly compensation (including a 40 percent load factor for benefits) of $55.72, the cost would be $1,337 ($55.72 per hour x 24 hours) per event.[11] The burden on individual firms would depend on the number of declarations they submit. The estimated annual burden to all declarants is $165,778 ($1,337 per event x 124 annual events).

We also considered a potential impact due to the numbers of patents listed. The proposed rule would require the submission of patent information

[11] Hourly rate for "lawyer" from the Bureau of Labor Statistics 2000 National Compensation Survey is $38.70, adjusted for inflation at 2.85 percent (unadjusted CPI–U) and 40 percent for benefits.

for patents that claim different forms of the drug substance, and this would appear to increase the number of patent filings. At the same time, the proposed rule would clarify the types of patents that must not be submitted, and this would appear to reduce the number of patent filings. These two countervailing effects are of uncertain magnitude. We cannot quantify an impact, if any, from a change in the number of patents listed, but we invite comment.

4. Enforcement Costs

The proposed rule, if finalized, can be enforced using existing resources.

5. Total Costs of the Regulation

The annual cost of the proposed rule includes the lost revenues to innovator firms from the erosion of market share, mitigated by the decrease in support costs, and the additional cost of completing the more detailed patent declaration. The estimated 1-year loss in revenues from erosion of market share is $3,159.50 million, the reduction in support costs would reduce this loss by $142.20 million, and the estimated annual additional cost of completing the revised declarations is approximately $166,000. Thus, the estimated 1-year cost to innovator firms is $3,017.47 million (approximately $3.0 billion).

According to projections produced by the Office of the Actuary at the Centers for Medicare and Medicaid Services, expenditures on prescription pharmaceuticals are expected to increase dramatically in the near future. This $3.0 billion 1-year estimate does not take these increases into consideration and must be adjusted to account for them. Prescription drug expenditures for 2003, for example, are expected to be 12.8 percent greater than for 2002.[12] After

[12] The annual percent increases in prescription drug expenditures for each year, 2003 through 2011, are assumed to be 12.8 (2003), 12.3 (2004), 11.7 (2005), 11.0 (2006), 10.7 (2007), 10.5 (2008), 10.3 (2009), 10.2 (2010), and 10.1 (2011). See National Health Care Expenditures Projections: 2001–2011, Centers for Medicare & Medicaid Services, Office of the Actuary, table 11.

using the average annual percent changes in prescription drug expenditures to adjust the annual cost, the total reduction in revenues to the innovator sector over the 10-year period 2002 through 2011 is estimated to be $51,507.55 million, or approximately $51.5 billion. Annualizing this impact over that 10-year period at a 7 percent discount rate yields an annualized cost of $4,863.76 million, or approximately $4.8 billion.

C. Benefits of the Regulation

This section develops estimates of the benefits from the proposed rule. Eliminating multiple 30-month stays per ANDA will prevent delays in generic drug competition. The 70 percent of the market lost by innovators is a gain to both generic drug companies and consumers. Generic drug companies gain through additional sales, and, to the extent that generic prices are lower than innovator prices, consumers benefit from the "price gap."

1. Gains to the Generic Drug Industry

We estimated the increase in sales to generic drug companies using the same model used to estimate losses in sales to innovators. Assuming typical drug peak sales to be $2.72 billion (including 2.0 frequency factor) and a typical delay of 23 months, the estimated increase in 1-year revenues to generic firms is $1,119 million (approximately $1.1 billion). After accounting for the baseline increases in pharmaceutical expenditures, the total increase in generic industry revenues for the period 2002 to 2011 is estimated to be $19,117.47 million or approximately $19.1 billion. The annualized cost, using a 7 percent discount rate is $1,805.23 million or approximately $1.81 billion.

While we recognize that the generic drug industry is doing more marketing than it used to do, the effort is still substantially smaller than what is done

by innovator firms, and we do not make adjustments for reductions associated support costs.

2. Gains to Consumers

The model assumes that after generic entry, the market will eventually stabilize where the price of a generic drug will be 33.5 percent of the equivalent innovator drug. The gain to consumers would be the difference between the generic and innovator price. This price gap is equal to 66.5 percent of the innovator price. Under our assumptions, the estimated consumer impact of the proposed rule is a 1-year gain of $2,040 million (approximately $2 billion). This gain would be from the elimination of multiple 30-month stays per ANDA that delay the availability of less expensive drugs.

After increasing this 1-year estimate to account for the annual expected increases in baseline pharmaceutical expenditures, the total expected benefit to consumers for the period 2002 to 2011 is $34,822.35 or approximately $34.8 billion. The annualized benefit to consumers, using a 7 percent discount rate, would be $3,288.21 or approximately $3.3 billion.

It is difficult to determine which subgroups of consumers will benefit most from access to generic drugs. The previously cited report on Pediatric Exclusivity noted that about 21 percent of pharmaceutical spending came from public sources (Federal, State & Local, Medicare and Medicaid) and that this figure was expected to rise. The report also noted that cheaper drugs would disproportionately benefit lower income consumers in that these consumers would be less likely to have insurance.

3. Other Issues Related to Benefits

In the past, some studies have allocated a portion of the gains to generic drugs to the distribution sector (e.g., retail drug stores). These studies typically

based this approach on the belief that generic drugs carried a substantially larger retail markup, in absolute dollar terms, than did innovator drugs.

This belief appears to be based on literature using limited data from the mid–1980s, a period when the generic drug industry was substantially different from its current state. For this analysis, we referred to more recent information, such as that found in the CBO report, and found no evidence of substantially larger absolute retail markup for generic drugs. While we believe recent data supports our belief that the absolute markups are approximately the same, we invite comment on this issue.

4. Total Benefits of the Regulation

The 1-year benefits of the regulation will include the increase in revenues to generic firms and the savings to consumers from the earlier availability of less expensive pharmaceuticals. The estimated total 1-year benefit is $3,159 million (approximately $3.2 billion). Adjusting this benefit to account for the expected increase in baseline pharmaceutical expenditures, the total benefit for the years 2002 through 2011 is expected to be $53,931.97 million or approximately $53.9 billion. Annualizing this stream of benefits over that 10-year period at a 7 percent discount rate yields an annualized cost of $5,093 million or approximately $5.1 billion.

TABLE 4.—BENEFITS OF THE PROPOSED RULE TO GENERICS AND CONSUMERS

Issue	One-Year Impact (Millions)
Generic Earlier Access to Market	$1,119.96
Consumer Drug Savings	$2,039.54
Total Benefits	$3,159.50

D. Comparison of Costs and Benefits

The estimated 10-year total costs of this proposed rule are $51,508 million. These costs would be borne by innovator firms in the form of reduced

revenues, mitigated by a reduction in support costs, and an increased cost of completing the revised patent declaration. The estimated annualized cost is $4,864 million.

The estimated 10-year benefits of this proposed rule are $53,932 million. These benefits would accrue to the generic drug firms and consumers in the form of increased revenues and increased income from access to cheaper drugs, respectively. The estimated annualized benefit is $5,093 million. Absent the additional cost of completing the declaration and the reduction in support costs, the costs equal the benefits because the economic impact of this proposed rule is a transfer, as consumers shift consumption from the products of the innovator drug firms to those of generic drug firms. The total 10-year quantified benefits exceed the costs by $2,424 million and the annualized benefits exceed the annualized costs by $229 million. While the quantified benefits do exceed the quantified costs, this proposed rule has the additional important benefit of preserving the balance struck in the Hatch-Waxman amendments.

E. Regulatory Alternatives

In creating this proposed rule, we considered several regulatory alternatives, including not regulating. We rejected the alternative of not regulating because under the current situation, NDA holders are able to use multiple 30-month stays to delay generic entry and thwart the intent of the Hatch-Waxman amendments. We also considered using the current system of patent declarations. This alternative was also rejected because the current declaration may be insufficient to prevent NDA holders and NDA applicants from listing patents that should not be listed under the law. This is particularly important in light of the fact that we lack the resources, expertise, and

authority to evaluate patents to determine whether they should be listed in the Orange Book.

F. Impact on Small Entities

Unless the agency certifies that the rule is not expected to have a significant impact on a substantial number of small entities, the Regulatory Flexibility Act, as amended by SBREFA requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. According to standards established by the Small Business Administration, a small pharmaceutical manufacturer employs fewer than 750 employees. We do not know the precise number of innovator companies expected to use multiple 30-month stays to delay generic entry. Nevertheless, we do not believe any of these innovator companies to be small. Moreover, none of the innovator companies identified in the FTC report as having used multiple 30-month stays would qualify as a small entity. Therefore, the agency certifies that this proposed rule is not expected to have a significant impact on a substantial number of small entities.

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 314 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

2. Section 314.52 is amended by redesignating paragraph (a)(3) as paragraph (a)(4) and by adding new paragraph (a)(3) to read as follows:

§ 314.52 Notice of certification of invalidity or noninfringement of a patent.

(a) * * *

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval. This paragraph also does not apply if the applicant amends its application to add a certification under § 314.50(i)(1)(i)(A)(*4*) when the application already contained a certification under § 314.50(i)(1)(i)(A)(*4*) to another patent.

* * * * *

3. Section 314.53 is amended by revising paragraphs (b) and (c)(1) through (c)(2) to read as follows:

§ 314.53 Submission of patent information.

* * * * *

(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 patents that claim the drug substance (ingredient), patents that claim the drug product (formulation and composition), product by process patents, and patents that claim a method of use. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents may not be submitted to FDA. For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the form of the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the "same" as the active ingredient that is the subject of the approved or pending application within the meaning of section 505(j)(2)(A)(ii) of the act. For patents that claim a 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. 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 that are the subject of a pending or approved application. For approved applications, the applicant shall identify the indication or other condition of use in the approved labeling that corresponds to the listed patent and claim identified.

(c) * * * (1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the declaration described in paragraph (c)(2) of this section for each claim of the patent that meets the requirements described in paragraph (b) of this section.

(2) *Patent declaration.* (i) For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), and/or method of use, the applicant shall submit the following declaration: This is a submission of patent information for an NDA submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act).

Time sensitive patent information pursuant to 21 CFR 314.53 for NDA #_____

The following is provided in accordance with section 505(b) of the Act:

Trade Name: _____

Active Ingredient(s): _____

Strength(s): _____

Dosage Form(s): _____

Approval Date (if the submission is a supplement to an approved NDA): _____

Please provide the following information for each patent submitted, and identify the relevant claim(s) by number.

A. 1. United States patent number: _____

2. Expiration date: _____

3. Name of the Patent Owner: _____

4. Agent (if patent owner or applicant does not reside or have a place of business in the United States) _____

B. For each patent identified in A, please provide the following information:

1. The type of patent claims that apply to the drug substance or drug product that is the subject of the application:

2. Drug Substance (Active Ingredient)

___ Yes ___ No

a. Claim number(s): _____

3. Drug Product (Composition/Formulation):

___ Yes ___ No

a. Claim number(s): _____

4. Method of Use:

___ Yes ___ No

a. Claim number(s): _____

C. For each drug substance claim identified, please provide the following information:

1. Is the claim one that claims the drug substance that is the active ingredient in the approved or pending NDA, an amendment to the NDA, or a supplement to the NDA?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

2. Is the claim one that claims a drug substance that is the "same" active ingredient as the active ingredient in the pending or approved NDA, amendment to the NDA, or a supplement to the NDA?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

3. If the answer to question C.1 or C.2 is "yes," do you acknowledge that an ANDA or 505(b)(2) application containing the same active ingredient that is claimed by the patent is the "same" for ANDA or 505(b)(2) approval purposes?

___ Yes ___ No

[*If the answers to questions C.1, and C.2, or C.3 is "no," stop here. The patent may not be listed in the Orange Book as a patent that claims the drug substance.*]

D. For each drug product claim identified, please provide the following information:

1. Is the claim one that claims the approved formulation or composition and/or the formulation or composition for which approval is being sought?

___ Yes ___ No

If "yes," please identify the claim(s) by number.

[*If the answer to question D.1 is "no" in every instance, stop here. The patent may not be listed in the Orange Book as a patent that claims the drug product.*]

E. For each method of use claim identified, please provide the following information:

1. Is the claim one that claims:

(a) an approved method of use of the approved drug product? If "yes," please identify the use with reference to the approved labeling for the drug product and identify the relevant patent claim number(s);

___ Yes ___ No

(b) a method of use of the approved drug product for which use approval is being sought; or

___ Yes ___ No

(c) a method of use of the drug product for which approval is being sought?

___ Yes ___ No

If the answer to questions E.1(b) or (c) is "yes," please identify the use with reference to the proposed labeling for the drug product and identify relevant patent claim number(s).

[*If the answers to questions E.1(a) through (c) are "no," stop here. The patent may not be listed in the Orange Book as a patent that claims a method of use.*]

(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 the patent claims that claim the drug substance, drug product, or method of use that has been approved.

* * * * *

4. Section 314.95 is amended by revising paragraph (a)(3) to read as follows:

§ 314.95 Notice of certification of invalidity or noninfringement of a patent.

(a) * * *

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval. This paragraph also does not apply

if the applicant amends its application to add a certification under § 314.94(~~b~~)(a)(12)(i)(A)(*4*) when the application already contained a certification under § 314.94(~~b~~)(a)(12)(i)(A)(*4*) to another patent.

* * * * *

Dated: SEP 26 2002

Lester M. Crawford,
Deputy Commissioner.

Tommy G. Thompson,
Secretary of Health and Human Services.

[FR Doc. 02–????? Filed ??–??–02; 8:45 am]

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