Federal Register

Wednesday,
June 18, 2003

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 314

Applications for FDA Approval To Market a New Drug: Patent Submission and 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; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 02N–0417]

RIN 0910–AC48

Applications for FDA Approval to Market a New Drug: Patent Submission and 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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its patent submission and listing requirements for new drug applications (NDAs). The final rule clarifies the types of patents that must and must not be submitted and revises the declaration that NDA applicants must provide regarding their patents to help ensure that NDA applicants submit only appropriate patents. The final rule also revises the regulations regarding the effective date of approval for certain abbreviated new drug applications (ANDAs) and certain other new drug applications, known as 505(b)(2) applications, submitted under the Federal Food, Drug, and Cosmetic Act (the act). In certain situations, Federal law bars FDA from making the approval of certain ANDA and 505(b)(2) applications effective for 30 months if the applicant has certified that the patent claiming a drug is invalid or will not be infringed, and the patent owner or NDA holder then brings suit for patent infringement. The final rule also states that there is only one opportunity for a 30-month stay in the approval date of each ANDA and 505(b)(2) application. The final rule will make the patent submission and listing process more efficient as well as enhance the ANDA and 505(b)(2) application approval processes.

DATES: *Effective Date*: This final rule is effective on August 18, 2003.

Compliance Date: The compliance date is December 18, 2003, for the submission of information on polymorph patents.

FOR FURTHER INFORMATION CONTACT: Jarilyn Dupont, Office of Policy and Planning (HF–11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3360.

SUPPLEMENTARY INFORMATION:

I. Introduction

This final rule revises implementing regulations in part 314 (21 CFR part 314) for certain statutory amendments to the act, 21 U.S.C. 301 *et seq.*, relating to new drug applications and generic drug approvals. The statutory provisions were added to the act through the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417 (21 U.S.C. 355, 360cc; 35 U.S.C. 156, 271, 282) (''Hatch-Waxman Amendments'')). These statutory provisions reflect an attempt to balance two competing interests: Promoting competition between ''brand-name'' or ''innovator drugs'' and ''generic'' drugs, and encouraging research and innovation. The act promotes competition by creating a process to expedite the filing and approval of ANDA and 505(b)(2) drug applications (applications submitted under the provisions of section 505(b)(2) of the act) and for resolving challenges to patents in court before marketing begins. At the same time, the act encourages research and innovation by protecting the patent interests of the patent owner and innovator drug company.

The final rule maintains a balance between the innovator companies' intellectual property rights and the desire to get generic drugs on the market in a timely fashion. The final rule limits to one per ANDA or 505(b)(2) application the maximum number of statutory 30-month stays of approval to which an innovator will be entitled when it submits multiple patents for the same NDA. Eliminating multiple 30-month stays will speed up the approval and market entry of generic drugs. The final rule also clarifies patent submission and listing requirements, which will reduce confusion and help curb attempts to take advantage of this process. Specifically, patents claiming packaging, intermediates, or metabolites must not be submitted for listing. Patents claiming a different polymorphic form of the active ingredient described in the NDA must be submitted if the NDA holder has test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.

A. What Are the Statutory Provisions Which Affect Patent Submissions and the Approval of New Drugs?

To explain why we (FDA) issued the proposal, we first describe how Federal law requires NDA applicants to file patent information and how that patent information can affect the approval of ANDA and 505(b)(2) applications. (We will refer to these as ''ANDA and 505(b)(2) applicants'' or ''ANDA or 505(b)(2) applicants'' and refer to their applications as ''ANDA and 505(b)(2) applications'' or ''ANDA or 505(b)(2) applications'' throughout the remainder of the preamble of this document.)

Section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) requires 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 (21 U.S.C. 355(c)(2)) imposes a similar patent submission obligation on holders of approved NDAs when the NDA holder could not have submitted the patent information with its application.

Under section 505(b)(1) of the act, we publish patent information after approval of an NDA application in our approved drug products list entitled ''Approved Drug Products With Therapeutic Equivalence Evaluations.'' This list is known popularly as the ''Orange Book'' because of its orange-colored cover. If patent information is submitted after NDA approval, section 505(c)(2) of the act directs us to publish the information upon its submission.

The act also requires ANDA or 505(b)(2) applicants to make certifications regarding each of the listed patents pertaining to the drug they intend to reference (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 (21 U.S.C. 355(b)(2)(A)(i) through (b)(2)(A)(iv) and 21 U.S.C. 355(j)(2)(A)(vii)(I) through (j)(2)(A)(vii)(IV)). 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) 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[1]), the act requires the applicant to notify the

[1] Paragraph IV throughout also refers to paragraph iv, the comparable provision in section 505(b)(2)(A) of the act.

NDA holder and patent owner (see sections 505(b)(3) and 505(j)(2)(B) of the act (21 U.S.C. 355(b)(3) and 355(j)(2)(B)). The notice states that an ANDA or 505(b)(2) application containing a paragraph IV certification to a listed patent has been submitted for the NDA holder's approved drug product (known as the ''listed drug''). The notice 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 the NDA holder or patent owner brings an action for patent infringement within 45 days after notice of the paragraph IV certification has been received, then we may not make the approval of an ANDA or 505(b)(2) application effective for 30 months, or such shorter or longer period as a court may order, or until the date of a court decision (see sections 505(c)(3)(C) and 505(j)(5)(B)(iii) of the act (21 U.S.C. 355(c)(3)(C) and 355(j)(5)(B)(iii)). (We will refer to the date the approval of an ANDA or 505(b)(2) application is made effective as the ''approval date'' throughout the remainder of this preamble.)

B. What Did the Proposed Rule Say?

In the **Federal Register** of October 24, 2002 (67 FR 65448), we published a proposed rule (proposed rule) that would address:

- The types of patents that must and must not be submitted by NDA applicants and NDA holders or patent owners (for purposes of this preamble, an NDA applicant is someone who is seeking FDA approval of a specific new drug application or supplement, whereas an NDA holder is someone whose NDA we have approved);
- The types of patents that we will list in the Orange Book;
- The patent declaration that NDA applicants must submit as part of an NDA, an amendment, a supplement, or when submitting information on a newly issued patent; and
- The 30-month stay of the effective date of approval for an ANDA or 505(b)(2) application.

The preamble to the proposed rule noted that, on occasion, we have seen NDA holders submit new patents for listing shortly before other listed patents for the same drug were to expire (see 67 FR 65448 at 65449). We explained that, in some disputes over recently listed patents, the parties had questioned whether particular patents met the regulatory requirements for submission and listing in the Orange Book. These disputes sometimes resulted in judicial decisions that are inconsistent with our regulatory policies or our interpretation of our own regulations (*id.*). We proposed to clarify our regulatory policies regarding patent submission, listing, certification, and notice. We also issued the proposal to respond, in part, to concerns raised by the Bureau of Competition and the Policy Planning Staff of the Federal Trade Commission (FTC). On May 16, 2001, the FTC submitted a citizen petition to FDA (FDA docket number 01P–0248) (''FTC Citizen Petition'') asking for 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 the FTC was conducting an extensive study of generic drug competition.

In July 2002, the FTC published the results of the study 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 claim the brand-name drug product. The FTC also recommended changing Federal law 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, the FTC asked us to issue a regulation or guidance clarifying whether an NDA holder could submit various types of patents for listing in the Orange Book. The types of patents for which the FTC sought clarification were patents that claimed metabolites, polymorphs, intermediates, product-by-process patents, and double patents (see FTC Report at pages A–39–A–45).

C. What Does This Final Rule Do?

The comments received expressed both support for, and opposition to, various provisions of the proposed rule. After careful review of these comments, we are making final most of the provisions of the proposed rule with certain modifications. The final rule:

- Allows a full opportunity for only one 30-month stay per ANDA or 505(b)(2) application;
- Prohibits the submission of patents claiming packaging, intermediates, or metabolites;
- Requires the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA;
- Adds a requirement that for submission of polymorph patents the NDA holder must have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA;
- Makes changes to the patent information required to be submitted and provides declaration forms for submitting that information to FDA, both with the NDA and after NDA approval; and
- Does not require claim-by-claim listing on the declaration form except for method-of-use patents claiming approved methods of use.

II. Comments on the Proposed Rule

We received over 35 comments on the proposed rule. The comments represented a diverse range of interests such as: Health insurance programs, brand name pharmaceutical companies, generic pharmaceutical companies, law firms, consumer organizations, pharmacy associations, the FTC, the New York Department of Health, large corporations, and individuals. In general, most comments supported the rule, either in whole or in part, and believed that the rule would help reduce prescription drug costs by making generic drugs available more quickly. However, other comments opposed the rule because they felt we had misinterpreted the act or because they felt that new legislation, rather than a regulation, was necessary. We describe the comments, and our responses to the comments, in this section. To make it easier to identify the comments and our responses, the word ''Comment'' in parentheses, will appear before the description of the comment, and the word ''Response'' in parentheses, will appear before our response. We also have numbered each comment to make it easier to identify a particular comment. The number assigned to each comment is only for organizational purposes. It does not signify the comment's value, importance, or the order in which we received it.

A. Comments on Specific Aspects of the Proposed Rule

1. What Patents Must and Must Not Be Submitted? (Section 314.53(b))

Proposed § 314.53(b) would require NDA applicants and holders or patent owners to submit information on the following types of patents for listing in the Orange Book. In brief, the proposed

rule would clarify that we would list only patents that claim:

- The drug substance (ingredient);
- The drug product (formulation and composition); and
- Method of use.

Proposed § 314.53(b) would not allow listing of process patents and patents claiming packaging, metabolites, or intermediates.

a. *Patents Claiming a Drug Substance—Must Patents that Claim the ''Same'' Active Ingredient Be Submitted and Listed*? For patents that claim a drug substance, the proposal stated that an 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.'' We explained that an NDA applicant or holder would determine whether the drug substance was the ''same'' as the active ingredient in the NDA by considering ''whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability'' (see 67 FR 65448 at 65452).

Drug substances that are the same active ingredient, but that are in different physical forms, are often called ''polymorphs.'' For example, the different crystalline forms of a drug substance are sometimes known collectively as polymorphs, and drug substances with different waters of hydration are sometimes referred to as ''polymorphs'' as well. (For purposes of this final rule, polymorphs include chemicals with different crystalline structures, different waters of hydration, solvates, and amorphous forms.) Under the proposed rule, an NDA applicant or holder would be required to submit a patent claiming a different polymorph from that of the drug substance described in the NDA if a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to dissolution, solubility, and bioavailability.

The proposed rule would make the patent listing standards generally consistent with the ANDA approval standards. For ANDA approval purposes, the active ingredient in a generic drug product can be the ''same'' as that in the reference listed drug notwithstanding differences in the physical forms of their active ingredient if the drug product performs the same. Thus, we stated that it would be consistent to interpret ''drug substance'' for patent submission and listing purposes as including certain drug substances having different physical forms if they would be considered the same active ingredient for ANDA approval purposes (*id.*).

We invited comment on whether we should revise the codified language to require an NDA holder to submit additional information regarding the basis for its assertion that the drug substances are the ''same'' active ingredient. We also invited comment on the potential impact of the change (allowing the submission of patents claiming different polymorphs) on the submission of ANDA and 505(b)(2) applications.

(Comment 1) Several comments disagreed with our proposal to allow listing of patents claiming different polymorphs of the active ingredient in the listed drug. Some comments stated that section 505(b)(1) of the act requires the patent to claim the drug substance that is the subject of the NDA. Several comments asserted that a patent claiming a polymorph that was not the subject of an NDA did not satisfy section 505(b)(1) of the act. Other comments argued that ''sameness'' for ANDA approval purposes differed from ''sameness'' in patent law, so we did not have to develop an identical interpretation of the two concepts. Several comments maintained that no such patents could exist if the active ingredients were truly the ''same'' because a subsequent patent for the ''same'' active ingredient should not have been issued. Some comments agreed that patents claiming different polymorphs of the same active ingredient should be listed, but only with submission of additional information such as clinical trial data required for FDA approval or proof that ''sameness'' is beneficial. A few comments maintained that the proposal did not change our pre-existing position because we have permitted NDA holders and applicants to submit patents claiming different polymorphs of the active ingredient. In response to our request for comment on the impact on ANDA and 505(b)(2) applications, one comment expressed the belief that listing patents claiming different polymorphs of the active ingredient would reduce the ability of generic manufacturers to ''design around'' the existing patents, an option which was contemplated by the Hatch-Waxman Amendments.

(Response) We decline to modify our position taken in the proposed rule which would require patents to be submitted for listing that claim different polymorphs of the active ingredient described in the NDA. If the NDA applicant or holder is able to establish that a polymorph claimed in a patent is the ''same'' active ingredient (i.e., that a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to such characteristics as dissolution, solubility, and bioavailability), the NDA applicant or holder must submit the patent to us for listing. We acknowledge that there may be some legitimate confusion regarding our prior position concerning submission of such patents for listing, which resulted in the listing of some polymorph patents in the Orange Book. The uncertainty over our policy resulted from certain court decisions, our response to those court decisions, and other public statements. The FTC Citizen Petition highlighted the need for clarification and is one reason we decided to implement this final rule and clarify our position. For the reasons explained in the preamble to the proposed rule (see 67 FR 65448 at 65452 to 65453), it is appropriate to have a consistent interpretation of the ''sameness'' principle in the patent listing and ANDA approval contexts. Accordingly, we will not treat polymorphs differently for patent submission and listings and ANDA approval. The argument that certain polymorph patents should never have been issued is not a matter for us to address. The Patent and Trademark Office (PTO) is responsible for reviewing and issuing patents. We will not question whether the PTO should have issued a particular patent, nor will we conduct a ''patent law'' or other analysis to determine ''sameness.''

We agree with the comments that suggested we needed to take additional steps to help ensure that the submitted patents claim the ''same'' active ingredient as that described in the NDA. A polymorph patent must claim the drug substance (active ingredient) to meet the statutory requirements for submission. We have modified the declaration requirement and created forms to help ensure that the NDA applicant or holder or patent owner confirms that the patent does claim the ''same'' active ingredient. The final rule and the declaration forms require that the NDA applicant or holder or patent owner certify that test data exist demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. If a patent claims more than one polymorph, each polymorph for which the required test data are available must be identified by claim or description in the declaration forms.

The final rule does not require these tests to be submitted to FDA at the time of patent submission, nor does it require the NDA applicant or holder to conduct the tests itself. The testing requirements, however, will ensure that only relevant polymorphs are submitted for listing.

Whether two different polymorphs are the ''same'' active ingredient for purposes of drug approval is a scientific determination based upon the specific characteristics of the forms of the drug substance involved. Only with testing can the scientific determination be made that the drug product containing the polymorph will perform the same as the drug product described in the NDA. The test data that the NDA applicant or holder or patent owner must certify exist at the time of patent submission are similar to the type of information required under §§ 314.50 and 314.94. The following explains more fully the required tests or data that would support the statement in the declaration forms:

• A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

• The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

• Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

• A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

• Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

This test data requirement corresponds to the test data required of ANDA applicants to demonstrate the drug product containing the polymorph described in the ANDA will perform the same as the drug product described in the NDA. In addition to the data requirements described in our regulations cited above (§§ 314.50 and 314.94), we have published guidance documents describing the test data ANDA applicants may use to demonstrate that the drug product will perform the same as the drug product described in the NDA. (See ''Guidance for Industry: Changes to an Approved NDA or ANDA'' (November 1999) and ''Guidance for Industry: Immediate Release Solid Oral Dosage Forms CMS 5'' (November 1995); these guidances are available at www.fda.gov/opacom/morechoices/industry/guidedc.htm.)

The stringency of these requirements regarding ''sameness'' also should address the concerns that the submission of polymorph patents might lead to submission of other patents claiming components which are not, but might be, included in a drug described in an NDA. Given the narrow legal and scientific basis for submission of polymorph patents, the final rule does not open the door to submission of any patents claiming formulations or inactive ingredients not contained in the drug product described in the NDA.

We believe that these changes will help deter submission of inappropriate polymorph patents. The assumption that a product containing a polymorph will perform the same as the product containing a different polymorph and described in the NDA will have to be substantiated.

b. *Product-by-Process Patents—Should These Patents Be Listed*?

Proposed § 314.53(b) would allow an NDA applicant or holder or patent owner to submit information on product-by-process patents. The act requires that NDA holders submit patents that claim the drug product. However, NDA applicants or holders must not submit patents that claim a process for making that product.

We explained that a product-by-process patent claims a product by describing or listing process steps to wholly or partially define the claimed product. In a product-by-process patent, the patented, novel invention is the product and not the process that is used to make the product. We recognized that the distinction between a product-by-process patent and a process patent might not be readily apparent to persons who are unfamiliar with patent law. We sought comment on ways to ensure that only appropriate product-by-process patents are listed in the Orange Book.

(Comment 2) Several comments argued that product-by-process patents must not be listed. Some comments stated that product-by-process patents ''closely resemble'' process patents and that the act does not allow listing of process patents. One comment asserted that listing product-by-process patents would have a ''profound negative effect'' on generic drug approvals because NDA applicants and holders or patent owners would attempt to list any product-by-process patent, whether or not the process defined in the patent was actually used to manufacture the drug product approved in the NDA.

Similarly, other comments sought to limit the type of product-by-process patents that could be listed. Several comments would revise the rule to require the product-by-process patent to claim a ''novel'' product, so that if the drug product described by the product-by-process patent was a ''known'' drug product or the product already had been listed in the Orange Book, we would not list the product-by-process patent. In other words, the comments sought to ensure that the product-by-process patent covered a product that was ''new and patentably distinct'' from previously-approved drug products. One comment suggested adding a new paragraph to the patent declaration to read as follows:

F. For each drug substance or drug product claim that was (1) identified as listable in subparts B and C and (2) is drafted in product-by-process format, please provide the following information:

1. Is the product of the recited process novel? [If the answer to question F.1 is ''no,'' stop. The patent cannot be listed. If yes, please identify the claim(s) by number.]

Another comment thought that few drugs would be the subject of a product-by-process patent. The comment recommended that we investigate any product-by-process patents that were listed in the Orange Book to see if these related to the NDA drug product. Yet another comment would amend the patent declaration to identify the product-by-process claims in the patent, the effective filing date of the patent application, whether the product has been previously sold, and, if the product had been previously sold, whether such sales occurred more than 1 year before the effective filing date of the patent application. The comment explained that if the drug's active ingredient has been previously sold for more than 1 year before the effective filing date of the product-by-process patent

application, the patent would be ineligible for listing because the patent would violate a specific provision in patent law.

In contrast, three comments supported listing product-by-process patents. These comments agreed that product-by-process patents are a form of a product patent. Two comments stated that we did not need to revise the rule to distinguish between product-by-process patents (which must be listed) and process patents (which must not be listed). The comment suggested revising § 314.53(b) to replace its mention of product-by-process patents with ''patents that claim the drug substance or drug product at least in part in terms of its method of manufacture (product-by-process patents).''

(Response) We agree that, to be submitted for listing, the product-by-process patent must claim the drug product that is the subject of the NDA. We explained in the proposed rule why a product-by-process patent is a type of product patent (see 67 FR 65448 at 65452). We also agree that the declaration should be clear enough to ensure that the patents that are submitted for listing are product-by-process patents and not process patents. In the response to comment 12 in section II.A of this document we detail the changes we have made to the declaration (including declaration forms) to help ensure that the patents submitted for listing are patents that claim the drug product that is the subject of the NDA and do not claim the process that is used to manufacture the drug product.

The declaration forms include a question which requires the NDA applicant or holder or patent owner to certify whether the patent being submitted is a product-by-process patent in which the product claimed is novel. Although we do not adopt the wording suggested by several comments, we agree that a requirement to identify the product as novel will help ensure that the patent is a product-by-process patent. We acknowledge that when the PTO issues a patent, the PTO necessarily determines that some aspect of the patent claims is ''novel.'' We want to make sure that the NDA applicant or holder or patent owner is identifying the product claim as the novel aspect. This clarification should eliminate the submission of patents that may be mistakenly identified as product-by-process patents but, in reality, are process patents which cannot be submitted for listing.

We expect that product-by-process patents will not be submitted often. Drug products approved under section 505 of the act typically are capable of being described by their chemical formula. Most such drug products approved are not of the type that can be described only in terms of the process used to produce the product. We decline to add any additional questions to the declaration relating to the patented product's length of time in the commercial market or other related questions, as we believe that the declaration questions we have added will accomplish the clarification necessary to prevent the submission of process patents.

c. *Patents Claiming Packaging—Do We Consider Containers and Delivery Systems to be ''Packaging*?'' Proposed § 314.53(b) would not have allowed an applicant to list a patent that claimed packaging.

(Comment 3) Most comments agreed that patents claiming packaging should not be submitted for listing. However, some comments stated that patents claiming devices or containers that are ''integral'' to the drug product or require prior FDA approval should be submitted and listed. These comments distinguished between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug.

(Response) We agree that patents claiming a package or container must not be submitted. Such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission. However, we have clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing.

Section 314.3 defines a ''drug product'' as ''* * * a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.'' The appendix in the Orange Book lists current dosage forms for approved drug products. The list includes metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems. The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not ''dosage forms.'' The revised declaration requirements, described in the response to comment 12 in section II.A of this document, detail the information required for submission.

d. *Patents Claiming Metabolites—Are Any Patents Claiming Metabolites Eligible for Submission and Listing*? The proposed rule would prohibit submission and listing of a patent claiming a metabolite of the approved drug. A metabolite is the chemical compound that results after the active ingredient of the drug has broken down inside the body. We explained that a patent claiming a metabolite does not claim the approved drug, as required by the act, because the metabolite exists only after the approved drug has been broken down inside the body (see 67 FR at 65451).

(Comment 4) Most comments agreed with our exclusion of patents claiming a metabolite. One comment, however, asked whether we would list ''a patent that claims a method of using an approved drug to administer a metabolite.'' The comment distinguished a method-of-use patent from a patent that claimed the metabolite.

(Response) The final rule prohibits submission of patents claiming metabolites when the metabolite is not the active ingredient described in the NDA. The submission of a metabolite patent does not meet the legal requirements for patent submissions as discussed in the proposed rule (see 67 FR 65448 at 65451). By contrast, if a patent submitted for listing claimed an approved method of using an approved drug to administer a metabolite, the submission of the patent would be permissible as long as all the conditions for submitting ''method-of-use'' patents are met. We describe the requirements for submission of method-of-use patents in the response to comment 7 in section II.A of this document. Briefly, if a method of use is described in the labeling for the drug product, and there is a patent claiming that method of use, the patent must be submitted for listing in the Orange Book, the method-of-use claim must be identified in the declaration forms, and the labeling language related to the method-of-use claim must be provided in the declaration forms.

e. *Patents Claiming Intermediates—Must We Allow Them to Be Submitted*? The proposed rule would not allow the submission of patents that claimed an intermediate. We explained that intermediates are materials that are produced during preparation of the active ingredient and are not present in the finished drug product. We consider intermediates to be ''in-process materials'' rather than drug substances or components in the finished drug product (see 67 FR 65448 at 65451 to 65452).

(Comment 5 and Response) The comments that addressed this issue agreed with the proposal. Consequently,

the final rule does not allow submission of patents that claim intermediates for the reasons explained in the proposal.

f. *''Double'' Patents—What Are They, and Must We Allow Them to Be Submitted*? The proposal did not discuss ''double'' patents.

(Comment 6) One comment suggested that we prohibit the listing of patents that contain a terminal disclaimer over a patent that had already been listed. The comment explained that patent law generally prevents an inventor from double patenting—that is, extending the term of the patent ''by the subsequent patenting of variations that are not patentably distinct from the first-patented invention.'' The comment stated that this ''double patenting'' can be cured if the patent holder files a ''terminal disclaimer'' which ''acts to disclaim the term of the later patent that extends beyond the term of the original patent, so that both patents expire on the same day.'' The comment expressed concern that NDA holders could list a later patent and have an opportunity to obtain a 30-month stay even if the later listed patent had a terminal disclaimer. In other words, the terminal disclaimer would prevent the inventor from enjoying a longer term of patent protection, but it would not prevent the imposition of another 30-month stay if the NDA holder or patent owner sued to enforce the later patent. The comment noted that, for the drugs PAXIL and FOSAMAX, the NDA holder had submitted earlier patents and a later-issued patent that had a terminal disclaimer. The patents were listed in the Orange Book, paragraph IV certifications were required for both patents and the NDA holder sued ANDA applicants on both patents, triggering 30-month stays.

(Response) We acknowledge that the ''double patenting'' described by the comment may, indeed, provide an NDA holder an opportunity to obtain an additional 30-month stay under the prior interpretation of the act. Under the final rule, there is no opportunity for multiple 30-month stays if patents with terminal disclaimers are submitted for listing. If such a patent is submitted after an ANDA applicant has filed a paragraph IV certification to a previously filed patent, and one full opportunity was provided for the 30-month stay, no notice need be given for a subsequent paragraph IV certification and no additional 30-month stay for that ANDA applicant can result under the final rule.

The act expressly contemplates listing of patents after NDA approval. It does not prevent an NDA holder or patent owner from submitting a patent with a terminal disclaimer. As long as the patent meets the statutory requirements, the patent must be submitted, even if it contains a terminal disclaimer. Again, we note that the PTO is responsible for the issuance of such patents. We defer to the PTO on matters of patent issuance.

g. *Method-of-Use Patents—Must the ''Use'' Be Approved in the Approved Drug Product*? The preamble to the proposed rule mentioned that patents claiming a method of use would be able to be submitted, but did not address such patents except to confirm our position that patents may not be submitted for listing if they claim methods of use that are not approved for the listed drug or are not the subject of a pending application.

(Comment 7) Comments disagreed as to whether the method-of-use claim in a patent submitted for listing must be a use approved in the NDA. Several comments urged us to list only those patents claiming methods of use approved in the NDA or that required clinical trials. One comment argued that listing only patents for approved uses was the only way to stop NDA holders from claiming broad uses or indications not in the approved labeling. In contrast, other comments argued that the act did not prevent NDA applicants or holders or patent owners from submitting patents for listing that claimed uses not approved by FDA. Some comments stated that patent infringement is not limited to approved uses. Other comments stated that section 505(b)(1) of the act contemplates the listing of patents claiming unapproved uses if a claim of patent infringement could reasonably be asserted, citing *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002) (*Purepac*).

(Response) If an NDA applicant or holder or patent owner intends to submit information on a patent that claims a method of use, the patent must claim a use that is described in the NDA. If we have already approved the NDA, the patent must claim a method of use that is in the labeling of the approved NDA. This has been our position since before we issued the final patent information rule in 1994 (see 59 FR 50338, 50363–50364 (Oct. 3, 1994)). The pre-existing requirement can be found at § 314.53(b) and (c)(2).

Sections 505(b) and (c) of the act support our position that only patents claiming approved methods of use be submitted for listing. Section 505(b)(1) of the act provides that the NDA applicant ''shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug * * * .'' The corresponding language in section 505(c)(2) of the act is nearly identical. Only method-of-use patents ''which claim the drug for which the applicant submitted the application'' must be listed. ''Drug'' is an ambiguous term, one which, for many years, we have consistently interpreted in the Hatch-Waxman Amendments to refer to the drug product. One court has said that:

> The meaning of the word ''drug'' in 21 U.S.C.§ 355(b)(1) cannot be determined apart from its context. Neither the FDA nor this court disputes that the definition of drug in § 321(g) covers both drug products and active ingredients. The relevant statutory section in this case, however, modifies the word ''drug'' by attaching the phrase ''for which the applicant submitted the application.'' In that context the FDA's interpretation of drug as meaning drug product is consistent with and indeed required by the statute.

(See *Pfizer, Inc.* v. *FDA*, 753 F. Supp. 171, 176 (D. Md. 1990).) All of the benefits afforded NDA holders under the Hatch-Waxman Amendments, such as the 30-month stay, derive from obtaining our approval of a particular drug product. Accordingly, only method-of-use patents that claim a use of the drug product in the pending or approved application must be submitted. Method-of-use patents for uses that the NDA holder ''has not chosen to make available to the public'' (*id.* at 177) must not be submitted for listing.

This construction of the statute is also supported by the more recent case law. Since we issued the proposed rule, there have been several judicial opinions discussing method-of-use patents. In *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), and in the related case *TorPharm, Inc.* v. *Thompson*, Civ. No. 03–0254 (D.D.C. April 25, 2003) (appeal pending for both *Purepac* and *TorPharm*), the district court held that, where a patent did not claim a use approved in the NDA, an ANDA applicant could not be required to certify to that patent, and the agency could properly find that no ANDA applicant was entitled to 180-day exclusivity on that patent. In *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), the Federal Circuit held that an ANDA applicant does not need to certify to a patent claiming a use not covered by the applicable NDA, and there is no cause of action against an ANDA applicant for patent infringement under 35 U.S.C. 271(e)(2)(A) for patents that claim an unapproved use. In *Allergan, Inc.* v. *Alcon Labs., Inc.*, 324 F.3d 1322 (Fed.

Cir. 2003), the Federal Circuit issued a per curium opinion that held that a method-of-use patent holder does not have an infringement action against an ANDA applicant when the use claimed in the patent is not FDA approved and the ANDA applicant is not seeking approval of that use. These decisions are consistent with our position that sponsors must not submit method-of-use patents that do not claim an approved use for listing in the Orange Book. They also highlight the need for an improved declaration that will clarify the claimed scope of the method-of-use patents being submitted.

We have modified the required declaration relating to method-of-use patents submitted. Although we agree, as discussed in the response to comment 11 of section II.A of this document, that each individual claim of a patent does not need to be listed on the declaration forms for drug substance and drug product patents, we do require identification of individual claims for method-of-use patents. The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use. This information will expedite our review of ANDA and 505(b)(2) applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can ''carve out'' the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.

The need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing is underscored by the decision in *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002). In that case, the NDA holder submitted information on a patent claiming what was later determined to be an unapproved use of the approved drug product. This submission was accompanied by the required signed declaration from the NDA holder that the patent covered the method of use for the approved product. Accordingly, we listed the patent and the use code information submitted with the patent. Years later, well after litigation over this patent was underway, the NDA holder clarified to FDA that the patent did not, in fact, claim the use for which the NDA was approved.

This submission of inappropriate patent information led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the act or a ''section viii'' statement under section 505(j)(2)(A)(viii) of the act. The section viii statement, which is also applicable to 505(b)(2) applications, permits the ANDA or 505(b)(2) applicant to avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent. A section viii statement does not carry the requirement for notice to the NDA holder and patent owner, and the related opportunity for a 30-month stay.

We have implemented the section viii provisions of the act by deferring to the NDA holder's or patent owner's assertion that the method-of-use patent claims an approved use of the drug product. When the NDA holder or patent owner submits a method-of-use patent for an approved NDA, we rely upon the requirements in the regulations and the required declaration as the evidence that the patent claims an approved use. Therefore, when an ANDA applicant has sought to duplicate the labeling for which the innovator has submitted the patent, and not to specifically omit, or ''carve out'' labeling, we require the ANDA applicant to submit a certification to that patent. A section viii statement would not be appropriate because the ANDA applicant is seeking approval for exactly the same labeling as that in the NDA for which the patent was submitted.

Our position has been that, for an ANDA applicant to file a section viii statement, it must ''carve out'' from the proposed ANDA labeling, the labeling protected by the listed patent. Unless the ANDA applicant can show that it is carving out certain method-of-use labeling, a section viii statement is not a correct submission for the listed patent. In *Purepac*, the court rejected our reliance on the regulations and the general declaration as a reasonable basis for this approach to implementation. The court specifically pointed to the patent submissions in the case, and noted that the NDA holder had not complied with the requirement that NDA holders submit only those patents claiming an approved use for the drug. Although the court noted that the facts in *Purepac* were unique (the NDA holder later admitted that it made its submission ''without regard'' to FDA's regulations), there may be other cases in which NDA holders have submitted patents claiming unapproved uses of approved drug products.

Following the *Purepac* decision, we have two options for implementing the section viii statement provisions under sections 505(b)(2)(B) and 505(j)(2)(A)(viii) of the act that intersect with the patent submission considerations described in the proposed rule. One approach would be to permit each ANDA and 505(b)(2) applicant to make its own independent decision on whether a listed method-of-use patent claims the use for which the ANDA applicant seeks approval, and then to submit a paragraph IV certification or section viii statement as the applicant sees fit. The second approach would be to require the NDA applicant or holder to identify specifically the approved uses claimed by the method-of-use patent, with reference to the approved labeling, and declare under penalty of perjury that the patent claims an approved use. This would permit ANDA and 505(b)(2) applicants, and us, to assess whether the ANDA or 505(b)(2) applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and thus determine whether the applicant must submit a patent certification or may submit a section viii statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the act.

In the absence of explicit statutory language, we believe an approach that requires the NDA applicant or holder or patent owner to identify the approved methods of use protected by the patent is most consistent with the general balance adopted in Hatch-Waxman. This approach permits the NDA applicant or holder to determine which patents claim its approved drug product and then, when appropriate, to resolve disputes over infringement of those patents through patent litigation. If ANDA and 505(b)(2) applicants could always avoid the possibility of a 30-month stay by asserting in a section viii statement that certain labeling for which the applicant is seeking approval is not protected by a listed method-of-use patent—despite the NDA holder's assertion to the contrary—there would be little reason for any applicant to submit a paragraph IV certification for a method-of-use patent. This approach would essentially eliminate the certification, notice, and litigation process as to any listed method-of-use patent, producing an outcome that is inconsistent with the act.

To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents. Since 1994, we have requested, but not required, that NDA applicants submit to FDA information on the approved use claimed by the patent. Since the

Purepac case and other instances have raised questions about what aspects of the approved drug are claimed by a listed use patent, we believe that it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we determine what submission is required of the ANDA and 505(b)(2) applicants referencing the approved drug.

We further note that we list methods of use for approved products in the Orange Book in the section on use codes. Due to the limitations of our database system and software constraints, we are limited to using 240 total characters for the use code description in the Orange Book. Traditionally, we have created the use code description for the Orange Book from the information submitted by the NDA applicant or holder. After considering the comments, and in light of the previously described litigation, we have determined that it is more efficient and accurate to ask the NDA holder to give us the exact use code description to be published in the Orange Book. Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. We understand that in some cases 240 characters may not fully describe the use as claimed in the patent. The declaration, which includes the complete description of the method-of-use claim and the corresponding language in the labeling of the approved drug, will be publicly available after NDA approval.

h. *Miscellaneous Patent Listing Comments*. i. *Should We Create an Administrative Process to Challenge Patent Listings or to De-List Patents or to Review the Listability of Patents*? The proposed rule did not propose an administrative process for challenging patent listings or for seeking removal of a patent from the Orange Book, nor did we propose a new process to internally review the patents for listability.

(Comment 8) Several comments stated that parties, such as generic drug companies and even third parties, need a method for challenging patent listings or for de-listing patents in the Orange Book. Some comments explained that the lack of an administrative procedure for challenging patent listings either encouraged NDA applicants to submit inappropriate patent information, or did not deter the practice, to delay generic competition. A number of comments maintained that FDA has more than a ministerial role and should review patents to determine if they meet the requirements for listing. Several comments contend that we have the authority to determine the attributes of the approved drug and thus to determine the appropriate patent listings. Various administrative mechanisms were suggested through which FDA could conduct a review of patents. These suggestions ranged from hiring patent lawyers to review submitted patents to development of a full administrative hearing process.

One comment stated that patent owners need an administrative process to enforce the listing of their patents because an NDA holder might ''fail'' to list eligible patents.

(Response) A fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents. The courts have the experience, expertise, and authority to address complex and important issues of patent law. This final rule supports that assumption in two ways. First, the final rule clarifies what patents must and must not be submitted for listing. This will make it easier for NDA applicants and holders and patent owners to avoid inadvertently submitting patents that do not meet the statutory and regulatory requirements. The clarification will reduce the pressure on us to intercede in patent listing disputes and will allow the courts and parties to focus on the ultimate issue of patent invalidity or non-infringement. Second, the final rule requires NDA applicants or holders or patent owners to submit detailed information and to certify to its correctness. This should further ensure that only patents meeting the statutory requirements will be submitted for listing.

We decline to create an additional administrative process for challenging patent listings beyond that already established in § 314.53(f). We also decline to create a new process for de-listing patents or for internal FDA review of patents beyond the limited review of the patent declaration described in this final rule. Section 505(b)(1) of the act directs NDA applicants to submit certain patent information. It requires that ''[u]pon approval of the application, the Secretary shall publish'' the patent information (emphasis added). In section 505(j)(7)(A)(ii) and (iii) the statute mandates that we publish revisions to this information every 30 days. These short time frames do not contemplate a substantive agency review of the scope of the patent and its application to the approved drug product. Indeed, the requirement of prompt publication (''upon submission''), combined with the 30-day timeframe for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.

In addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority. Although we will continue to relay questions about the accuracy of a patent submission to the NDA holder (see § 314.53(f)), our patent listing role remains ministerial. Courts have upheld our determination that our role with respect to patent listing is ministerial. (See *aai Pharma* v. *Thompson*, 296 F.3d 227, 242–43 (4th Cir. 2002), cert. denied, 123 S. Ct. 1582 (2003); *American Biosci., Inc.* 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*, 194 F. Supp. 2d 442, 445–446 (D. Md. 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).) We recognize that one court has held that parties have no private right of action to seek de-listing of patents (see *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001)). Nevertheless, it would be inappropriate and impractical for us to create regulatory mechanisms for reviewing patent listings or permitting third parties to submit patents for listing. We lack both the resources and the expertise to resolve such matters.

Furthermore, even if we were to establish an administrative process for patent review, our decisions on these patent listing matters would inevitably lead to disputes and increased litigation against us. This litigation could question whether such an administrative process was within our legal authority. Even if the courts were to decide that we may review submitted patents, there would be repeated litigation over individual patent listing decisions. Given the uncertainty of the listing status of the challenged patent during the litigation, there is no assurance that, if we reviewed submitted patents, ANDAs or 505(b)(2) applications would be approved sooner and generic drugs would enter the market any more rapidly.

We agree that there have been a few cases in which legitimate concerns have been raised about whether specific submitted patents meet the statutory requirements for submission and listing. We believe that these concerns will be adequately and efficiently addressed by the clarification of the types of patents that must and must not be submitted and by improvements to the patent information required. We further believe that even if legally permissible, it is not necessary for us to develop a patent review mechanism. The final rule permits us to allocate our limited resources to public health activities, while leaving questions of patent law to the courts, which are better able to handle such questions. This division of responsibility is fully consistent with the process established in the Hatch-Waxman Amendments.

(Comment 9) One comment suggested that we create an administrative mechanism to ensure timely patent infringement litigation if no statutory notice is provided to the NDA holder.

(Response) We decline to amend the proposed rule as suggested by the comment. The act does not contemplate that we will play an active role in determining the timing of patent infringement litigation. In the absence of the 45-day timetable imposed when notice is given for a paragraph IV certification, a decision on whether and when to file suit for patent infringement may depend on multiple variables. For example, did the NDA holder or patent owner have sufficient information to decide whether to sue the ANDA or 505(b)(2) applicant for patent infringement? An ANDA applicant and the NDA holder may disagree on when the NDA holder had sufficient information to decide to file suit. The parties may also disagree as to what constitutes ''timely'' litigation. For example, an NDA holder who defers filing a lawsuit on a later-filed patent until a 30-month stay has elapsed may feel that the subsequent litigation is still ''timely,'' given the information available to the NDA holder. The ANDA or 505(b)(2) applicant may view this latter lawsuit as an obstacle to marketing its drug product. Given the limits of our statutory authority as well as complex issues of patent litigation strategy that lie outside our expertise, we decline to create a mechanism to ensure ''timely'' patent litigation in situations where the NDA holder and patent owner did not receive notice of subsequent paragraph IV certifications.

ii. *Should There Be Time Limits on Patent Submissions or Certifications*? The proposed rule did not specify when patent information would need to be submitted, or whether ANDA or 505(b)(2) applicants would need to provide certifications for patents listed after they had filed an ANDA or 505(b)(2) application.

(Comment 10) Several comments suggested revising the rule to create time limits relating to the submission of patent information or patent certifications. For example, one comment asserted that ''abuse'' occurs when NDA holders submit non-meritorious patent information to us shortly before an earlier-submitted patent is to expire. Another comment suggested that we limit the time during which NDA holders can submit patent information to a defined time period after we have approved their NDAs. Another comment said we should not require ANDA applicants to submit amended patent certifications if the patent was submitted after the first ANDA had been filed.

Similarly, one comment asserted that a patent submitted after NDA approval cannot claim the approved drug product because the later-submitted patent would be invalid. The comment explained that, under patent law, a person cannot obtain a patent if the subject of the patent is known and therefore ''anticipated'' under patent law.

(Response) We decline to amend the proposed rule as suggested by the comments. The act clearly contemplates the submission of additional patent information after an NDA has been filed. For example, section 505(b)(1) of the act instructs applicants to amend their NDAs to include information on a patent issued after the NDA has been filed, but before the NDA has been approved, which claims the drug or a method of using the drug that is the subject of the application. Section 505(c)(2) of the act directs NDA holders to submit patent information if the patent issued after we have approved the NDA. We do not interpret the act as permitting us to refuse to accept submissions of new patents either after an NDA has been filed or approved, or after an ANDA has been submitted.

Section 505(c)(2) of the act also instructs NDA holders to submit information on patents issued after NDA approval no later than 30 days after the date the patent issued. This deadline ensures prompt public notice that the NDA holder believes the patent claims the approved drug product and permits legal issues regarding these later-issued patents to be resolved as early as possible. Under § 314.94(a)(12)(vi), we do not require an ANDA or 505(b)(2) applicant with a pending application to certify to a patent issued after NDA approval but not submitted to us within 30 days after issuance. However, the patent will be listed in the Orange Book upon submission of a complete declaration, and ANDA and 505(b)(2) applications filed after the patent is listed will be required to contain a certification to the patent. This longstanding interpretation is consistent with the statutory language describing patent submission deadlines, the notice concept inherent in patent publication, and early judicial resolution of patent disputes. We are not persuaded by the comments that we should change our interpretation.

We believe that removing the possibility of multiple 30-month stays per ANDA will diminish the incentive to obtain additional patents late in the patent life of the product described in the NDA. As described in the FTC Report, of the patents reviewed by FTC, many of the patents submitted well after NDA approval, and usually after an ANDA application was filed, were ultimately found to be invalid. Therefore, in the absence of the 30-month stay, these patents would have been unlikely to serve as a basis for a preliminary injunction precluding market entry of generic drugs.

We also decline to amend the proposed rule to exempt ANDA applicants from submitting patent certifications if the patent was listed after the ANDA was filed. Our pre-existing regulations do not require ANDA applicants to amend their patent certifications if:

- The NDA holder failed to provide the required patent information within 30 days after the issuance of the patent; and
- The ANDA had already been submitted and had contained an appropriate patent certification before the submission of new patent information (see § 314.94(a)(12)(vi)).

However, if the NDA holder has submitted patent information in a timely manner, consistent with section 505(c)(2) of the act, then section 505(j)(2)(A)(vii) of the act requires the ANDA applicant to certify to that patent. Section 505(j)(2)(A)(vii) of the act requires ANDA applicants to provide a certification with respect to ''each patent which claims the listed drug,'' not only patents that are listed at the time the ANDA is submitted. The act contemplates the submission of patent certifications even if the patent was listed after the ANDA or 505(b)(2) application had been submitted.

We do not have the authority to declare any patent to be invalid. We leave questions regarding the issuance

and validity of patents to the PTO and the courts.

iii. *What Should the Patent Declaration Say*? (Proposed § 314.53(c)). Proposed § 314.53(c) would require a patent declaration for NDA applicants and holders and patent owners to complete as part of the NDA, an amendment, a supplement, or for information on a later-issued patent. The proposed revised declaration in the proposal was a ''checklist'' that focused on individual patent claims. The proposed declaration required information on each claim to help ensure that applicants submit only appropriate patent information, and that they stand behind the accuracy of the information. The proposed requirement to identify claims was intended to help all parties focus on the same claim and help prevent arguments as to whether a particular claim claimed the approved drug product.

(1) *Should the Declaration Identify Individual Patent Claims*?

(Comment 11) Several comments objected to identifying patent claims as part of the declaration. The comments stated that a claim-by-claim listing:

• Would be ''unnecessarily onerous'' because patents may contain many claims;

• Could threaten the patent holder's legitimate rights if the NDA applicant failed to list a patent claim because the failure to list that claim could be used as an admission against the NDA holder's or patent owner's interests in litigation;

• Could expose the NDA holder to criminal and civil liability if the claim cited in the declaration is later found not to claim the drug; or,

• Is irrelevant to patent listing because the patent, and not the patent claims, is what we must list in the Orange Book.

Other comments supported the claim-by-claim listing. Some comments requested that we impose a 30-month stay only if the specific claims submitted in the patent declaration were the subject of the patent litigation filed within the 45-day time period.

(Response) We have re-examined our rationale for proposing a claim-by-claim listing and have concluded that submission of a claim-by-claim declaration for all patents is not warranted. Such detailed information is not explicitly required by the act and is not necessary for a patent to be listed in the Orange Book. Section 505(b)(1) of the act requires that the patent be one that ''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 * * *.'' The number of claims contained within a particular patent does not affect the ability of the patent to be listed as long as there is at least one claim that meets the two required elements.

Individual patent claims are relevant for purposes of the Orange Book only in the context of method-of-use patents. The specific method-of-use claims are essential to our review because sections 505(j)(2)(A)(viii) and 505(b)(2)(B) of the act allow ANDA and 505(b)(2) applicants to file statements which assert that the method-of-use patent does not claim a use for which the applicant is seeking approval. The ANDA or 505(b)(2) applicant does not have to seek approval for all uses approved for the reference listed drug. Thus, the claim-by-claim listing of method-of-use patents will permit ANDA and 505(b)(2) applicants to assess whether they are seeking approval for a use claimed in the listed patent, and thus determine whether to submit a patent certification or a section viii statement. Additionally, we can verify that the certification or statement is correct, and that only the appropriate methods of use are included in the proposed labeling for the ANDA or 505(b)(2) drug product.

We decline to adopt the recommendation made in some comments to require all claims to be listed and then provide a 30-month stay only for litigation involving a claim listed in the Orange Book. This suggestion would require us to significantly exceed our ministerial responsibility in listing patents because we would be obliged to evaluate patent lawsuits and their relation to individual patent claims. We discuss our ministerial role in the response to comment 8. Removing the proposed requirement of a claim-by-claim listing in the final rule should not be detrimental to ANDA or 505(b)(2) applicants. In fact, several generic companies, the FTC and the Generic Pharmaceutical Association (GPhA), stated in their comments that no ''prudent generic company'' would rely solely on Orange Book listings to evaluate patent information for litigation exposure, particularly when all patents cannot be listed in the Orange Book. Thus, we believe that identification of the relevant patent(s), as opposed to the individual patent claims (other than for method-of-use patents), satisfies the act's explicit requirements, provides sufficient information to potential applicants to determine if a more thorough patent search or analysis is warranted, and will help to ensure appropriate patent submissions.

(2) *Should the Declaration Be Expanded or Modified*? The proposed rule would revise § 314.53(c)(2) and would replace the existing, general declaration with a more detailed declaration. The proposed declaration would be a ''checklist'' that required information on the approved drug product including trade name, active ingredient(s), strength(s), dosage form(s), and approval date. For each patent submitted, each claim of a patent which applied to the drug substance (active ingredient), drug product (formulation or composition), and method of use would need identification. A ''yes'' or ''no'' check-off would be required as to each individual applicable patent claim. The proposed § 314.53 would require the NDA applicant or holder or patent owner to state in the declaration that the information was provided for an NDA submitted under section 505 of the act.

(Comment 12) Several comments supported our proposed changes to the declaration but also suggested additions to the declaration. These comments would add the following information to the declaration:

• Specific exclusions of patents for forms of the active ingredient not marketed, such as acids, freebases, salts, and isomers;

• Exclusion of patents claiming labeling matters such as business methods, registries, titration/dosing schedules, or ornamental designs;

• Exclusion of a patent claiming a drug substance claimed in conjunction with another active ingredient or method of using the combination which is not the claimed drug substance;

• Various forms of statements indicating or certifying the submitter has filed accurate information;

• Identification of the NDA applicant's pending patent applications; and

• Additional information for product-by-process patents.

The comments suggested that it was necessary to identify each of the excluded patents in the declaration form and the codified text. Several comments suggested requiring a sworn statement and an acknowledgement that a false statement was subject to criminal penalties. For example, one comment suggested that the declaration include the statement: ''The undersigned declares that all of the above information has been provided in accordance with Title 28, section 1746, entitled 'Unsworn declarations under penalty of perjury','' followed by the signature, date, title, and telephone

number. The comment also would require additional information on patents in the declaration form to identify that the product in the product-by-process patent was a novel product.

(Response) We agree, in part, with the comments that the information that would be required in the declaration should be modified. Also, we have created standardized declaration forms which will encompass the required patent declaration information.

The final rule changes the general requirements in pre-existing § 314.53(c)(1) by requiring that the patent information which must be submitted must be provided on the declaration forms in full. In final § 314.53(c)(2), we substitute declaration forms which must be used in place of the checklist described in the proposed rule. Each declaration form is a standard form that must be used by all NDA applicants or holders or patent owners for submission of patent information at the time of initial NDA or supplement filing, and upon and after NDA or supplement approval.

For several years our Internet Web site has included a sample format which can be used in submitting patent information required under pre-existing regulations. Although use of the sample format is purely voluntary, it is used extensively to submit patent information to us. Based on this experience, and given the additional information required in the final rule, we concluded that mandatory declaration forms are appropriate to obtain the patent information. We, thus, require use of forms in the final rule. Since we determined that forms are appropriate, we have consolidated information currently required by pre-existing regulations with the new required information. For example, we require a response on whether there are relevant patents related to the drug product, information currently required under pre-existing § 314.53(c)(3). This was not contained in the proposal but, for administrative efficiency, and to lessen the burden on NDA applicants or holders or patent owners, we have included in the declaration forms all of the required information relating to the patent submission.

The NDA applicant must provide a declaration form when an NDA, amendment, or supplement to an NDA is filed. The NDA holder must also submit another declaration form after NDA or supplement approval to provide information on all patents relevant to the approved NDA or supplement, whether or not information on any such patent was previously submitted. The declaration forms filed with us must be attested to as to the accuracy of the patent information being submitted. Examples of the two declaration forms, FDA Form 3542 and 3542a, are provided in the Appendix found at the end of this document. The declaration forms will be available on the Internet at http://www.fda.gov by searching for the word ''forms''.

The final rule also revises pre-existing § 314.53(c)(2)(ii) and (c)(3) to conform to the changes we made to the patent information required on the declaration forms. The final rule requires a declaration form to be filed with us within 30 days after NDA approval; this is consistent with the pre-existing requirement. This form must also be used to file patent information on any patents submitted or issued after NDA approval. This declaration form requires the NDA holder or patent owner to provide the patent information applicable to the approved NDA. It is similar to the declaration form filed upon the filing of an NDA, supplement, or amendment. However, the declaration form filed upon or after NDA approval requires information on the approved product and a description of the approved methods of use for the use code listing in the Orange Book. This description will be limited to 240 characters as discussed in the response to comment 7.

The final rule describes other information required for the declaration forms not identified in the proposed rule. Some of the additional information will allow us to more easily determine the eligibility of the patent for listing, while other information will provide more complete information related to the responsibilities of the NDA holders or ANDA applicants. For example, we require the issue date of the patent in order to determine whether the patent has been submitted to us within the required 30 days. We require information on whether the patent being submitted has been submitted previously for the NDA or supplement referenced in the declaration. For example, an earlier listed patent may have included several method-of-use claims but only one method of use previously approved and submitted. A second method of use may be approved in a supplement and must be submitted for listing. Such information will assist the Orange Book staff with its administrative listing responsibilities. The address and contact information of the patent owner required in the declaration forms will assist in the required notification to the patent owner of a paragraph IV certification. We have elaborated on the requirement for asserting that the polymorph is the ''same'' as the active ingredient approved in the NDA. We require information on whether the patents submitted claim metabolites or intermediates to help ensure that the patents prohibited from submission under final § 314.53(b) are not submitted. Similarly, we require information on patents claiming the drug product to prevent the submission of patents claiming packaging.

The final rule also requires information on product-by-process patents as discussed in the response to comment 2 of section II.A of this document. We have added a requirement that the NDA applicant or holder or patent owner state whether the patent being submitted is a product-by-process patent in which the product claimed is novel. This is to help ensure that process patents are not submitted for listing.

We agree that the attestation in the declaration form should be revised in the final rule. In the proposal, we stated that we had revised the declaration so that applicants would ''make careful and well-considered representations'' and ''stand behind the accuracy of that information'' (see 67 FR 65448 at 65453). In the final rule, we revise the statement to be more specific about the need to ensure the information is accurate. We adopt the attestation statement contained in 28 U.S.C. 1746 for unsworn declarations and include attestations in the declaration forms. The attestation statements in the declaration forms read as follows:

(Declaration Form 3542a submitted with NDA, amendment or supplement.)

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

(Declaration Form 3542 submitted upon or after NDA approval.)

The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

We also include a warning statement in the declaration forms to alert the submitter that a willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

We decline to revise the proposed rule to list every excluded type of patent as requested by some comments. Based on our experience, we believe that if we attempted to include questions on all types of patents, such as ''business method'' or ''registry'' patents, or specifically list all exclusions in the final rule, there would be disagreements over whether the examples are all-inclusive or whether other types of patents were excluded as well. We believe the patent information requested is sufficient to ensure only eligible patents are submitted for listing.

We also decline to revise the declaration to require identification of an NDA applicant or NDA holder's patent applications that are under review by the PTO. The act does not contain any references to pending patents. In contrast, sections 505(b) and 505(c)(2) of the act contain requirements for patent information to be submitted after the patent is issued. Section 505(b) of the act requires that the information submitted on any patent claiming the drug include the patent number and expiration date of the patent. We publish that information when we list the patent in the Orange Book. A patent number and expiration date are available only when the PTO issues a patent and are not available for pending patent applications. Accordingly, we will not require submission of information regarding pending patent applications.

Although we do not require submission of information concerning pending patent applications, we understand that pending patent applications are generally publicly disclosable by the PTO if pending for more than 18 months at the PTO or foreign patent offices. In addition, information concerning pending patents would not provide any useful information if the PTO never issued the patent.

We note that we will not evaluate a patent to assess whether the declaration is accurate or whether the patent has been appropriately submitted for listing (see our response to comment 8). We will, however, review the declaration for completeness and to determine that the information given by the NDA applicant or holder or patent owner indicates that the patent is eligible for listing.

Although section 505(b)(1) of the act requires submission of patent information upon the filing of an NDA, we will rely only on the declaration form filed upon or after NDA approval under § 314.53(c)(2)(ii) to list patent information in the Orange Book. Patent information for newly approved NDAs, NDA supplements, or newly issued patents will not be published in the Orange Book unless and until we receive a complete declaration submitted post-NDA approval indicating the patent is eligible for listing.

We interpret the statute to permit listing of only those patents claiming the approved drug product and its approved uses. Even though the NDA applicant must submit patent information prior to NDA approval, it is not until the NDA or supplement has been approved that the scope of that approval is known. For example, we might approve only one of two indications proposed in an NDA and, thus, patents on an unapproved indication or use, although submitted with the original NDA, could not be listed. Therefore, as a way of confirming or amending the original patent information, a declaration form must be submitted after approval. If the declaration form submitted after NDA approval is incomplete or indicates a patent is not eligible for listing, we will notify the NDA holder and indicate the reason. The NDA holder must resubmit the declaration form with complete information indicating that the patent is eligible for listing. If the declaration form is incomplete or indicates the patent is not eligible for listing, we will refuse to list the patent until an appropriate declaration form has been submitted.

For patents newly issued by the PTO after the NDA is approved, section 505(c)(2) of the act requires that the NDA holder submit the patent information to us within 30 days to be considered timely filed. All such patent information must be contained in a complete declaration submitted post-NDA approval indicating that the patent is eligible for listing. A patent is considered listed in the Orange Book as of the date it is received in the Central Document Room as required in § 314.53(d)(4) and (d)(5), if it is accompanied by a declaration form that is both complete and contains information indicating that the patent is eligible for listing. If we must notify an NDA holder that a declaration form is incomplete or the patent is not eligible for listing, and the NDA holder then submits an acceptable declaration within 15 calendar days, we will consider the patent timely filed. So, for example, suppose an NDA holder submits information on a new patent to us 20 days after the patent is issued by PTO, and we notify the NDA holder 5 days later that the declaration is incomplete. If the NDA holder submits an adequate declaration within 15 calendar days of the notification, we will consider the patent information to have been submitted as of the date we originally received it, that is, within the 30 day period allowed by the statute. If the NDA holder submits the adequate declaration more than 15 calendar days after notification, we will consider the patent information to have been submitted on the day the revised declaration form is received, which may be more than 30 days after the date of patent issuance. Such patents will be subject to patent certification only as described in § 314.94(a)(12)(vi). If the NDA holder does not submit an adequate declaration for the newly issued patent, we will not list the patent in the Orange Book. This approach is appropriate because it gives the NDA holder who promptly submits information on a newly-issued patent a reasonable period of time to correct a mistake in a patent declaration, while at the same time ensuring that there are adequate declarations and minimal delays for listed patents. We will accept certifications to any patent only from the date an acceptable declaration is submitted.

The process established in § 314.53(f) for patent listing challenges is not altered by our requirements for patent information and declaration forms. Interested parties may still rely on that process if they believe a patent has been submitted and listed in error.

We are aware of NDA holders that have submitted patents for listing that have been listed in the Orange Book and then, at a later time, been removed from the Orange Book at the NDA holder's request. If, after the patent has been removed from the Orange Book, the NDA holder again seeks to submit the patent for listing, we will require resubmission of the patent information and the filing of an accompanying patent declaration before the patent will be relisted. Such resubmission will be governed under the final rule. If the resubmission of a previously listed patent takes place after the effective date of this rule, the final rule applies as described in section IV of this document.

The final rule does not require us to review or evaluate patents, but will simplify and clarify the submission process for NDA applicants and holders and patent owners, and will promote administrative efficiency. The additional information required by the declaration form will help ensure that only appropriate patents are submitted for listing.

2. How Many Times Can an ANDA or § 505(b)(2) Application's Approval Date Be Delayed by 30-Month Stays?

The proposed rule offered an interpretation of the act that would limit the number of 30-month stays to only one possible stay per ANDA or 505(b)(2) application. The proposed interpretation in the proposed rule differed from our previous interpretation of the act (which allowed for multiple 30-month stays). Under our proposed interpretation, the ANDA or 505(b)(2) applicant would continue to file the appropriate certifications as required under section 505(j)(2)(A)(vii)(I) through (j)(2)(A)(vii)(IV) or section 505(b)(2)(A)(i) through (b)(2)(A)(iv) of the act. However, under the proposed interpretation in the proposed rule, the notice to the NDA holder and patent holder of the paragraph IV certification is required only when a paragraph IV certification is included in the initial ANDA or 505(b)(2) application or when such an application is amended to include, for the first time, a paragraph IV certification. Notice to the NDA holder and patent owner is one of the requirements for a 30-month stay; if the ANDA or 505(b)(2) applicant is not obliged to provide a subsequent notice to the patent owner and NDA holder, no successive 30-month stay is possible.

a. *When Must Notice Be Provided and What Is a Full Opportunity for a 30-Month Stay*? The proposed rule would require an ANDA or 505(b)(2) applicant to provide notice to NDA holders and patent owners only when the applicant files a paragraph IV certification with the initial application or amends the application to include a paragraph IV certification for the first time. If the application were amended to add additional paragraph IV certifications, no notice to the NDA holder and patent owner would be required.

(Comment 13) Several comments claimed that the lack of notice for subsequent paragraph IV certifications would delay initiation of patent litigation. To avoid this ''delay,'' the comments suggested that, if we retained our proposed interpretation allowing only one 30-month stay per ANDA or 505(b)(2) application, we should amend the rule to:

- Give the ANDA applicant the ''option'' to provide voluntary notification;
- Give the ANDA applicant the ''option'' to provide notification and be subject to an ''optional'' additional 30-month stay;
- Require us to notify the NDA holder as to a subsequent paragraph IV certification.

Similarly, several comments expressed concerns that ANDA and 505(b)(2) applicants could manipulate the rule to avoid even a single 30-month stay. The comments explained that in the absence of notice for all paragraph IV certifications, there could be several scenarios in which an ANDA or 505(b)(2) applicant could take advantage of the regulations to avoid a meaningful 30-month stay under our revised interpretation. For example, an ANDA or 505(b)(2) applicant could file a paragraph IV certification on a narrow patent or a narrow patent claim and provide notice to the NDA holder and patent owner on that certification, thereby satisfying the regulatory requirements, while providing a paragraph III certification on broader patents or claims. The NDA holder or patent owner could bring a patent infringement suit within the 45 days, triggering a 30-month stay, or decide not to bring suit on the narrow claim or patent. The comments argued that, after suit was filed, or after the 45 days expired with no suit initiated, the ANDA or 505(b)(2) applicant could change the paragraph IV certification to a paragraph III. If suit had been filed, the applicant could seek dismissal of the patent infringement suit and avoid the 30-month stay. At a later date, the ANDA or 505(b)(2) applicant could change its paragraph III certification on the broader patent or claim to a paragraph IV certification, but because there had already been an opportunity for a 30-month stay, no further 30-month stay would be possible.

The comments maintained that we should not allow such manipulation and that it could be avoided by treating the new or revised certification as though it relates back to, and substitutes for, the original certification so that the notification requirements for original applications, and not those for amendments, apply. Under this suggested approach, the changed paragraph III certification would be treated as if the original application had contained the paragraph IV certification. The new certification, thus, would require notice to the NDA holder and patent owner and have the potential to trigger a 30-month stay. The comment cited § 314.94(a)(12)(viii) which relates to amended certifications to support this approach. In this instance, it was argued that there should be the opportunity for at least one 30-month stay when the ANDA or 505(b)(2) applicant ''alters or amends'' a patent certification for reasons other than the listing of a patent subsequent to the filing of an ANDA.

(Response) We decline to modify the proposed rule as suggested. We conclude, however, that clarification of the proposed rule is required in the final rule to ensure that our revised interpretation allows for one full opportunity for a 30-month stay after notice of a paragraph IV certification.

Our long experience with administering the Hatch-Waxman Amendments convinces us that any regulatory scheme in this area will be complex, and that any advantage that a party can find in manipulating the regulatory program will be pursued. Despite our conviction that the final rule will substantially reduce such manipulation, we do not believe we can completely prevent attempts at ''creative compliance'' by the parties.

Our revised interpretation of the statute reads all three subparagraphs of section 505(j)(2)(B) of the act as a coherent whole. We believe that Congress considered the first paragraph IV certification, notice and the opportunity for a single 30-month stay, to be part of an inter-connected process. In the final rule we keep these provisions operating together, as much as possible, requiring that certifications be made and notification provided in such a way that there always will be one full opportunity for a 30-month stay.

The notice requirement in the final rule depends on whether the ANDA or 505(b)(2) application contained a paragraph IV certification before the submission of an amendment containing a paragraph IV certification. We note three potentially confusing situations concerning applicability of that principle and describe how these will be treated under the final rule.

First, an ANDA or 505(b)(2) applicant who filed a paragraph IV certification could change to a paragraph III certification after notice is given but before the 45 days for filing suit has run and before a suit is filed. In this situation, because the opportunity for a 30-month stay has not vested (the 45 days has not expired or patent litigation has not yet been initiated), under the final rule, this ANDA or 505(b)(2) application will not be considered to have ever included a paragraph IV certification. If a paragraph IV certification is submitted later, the notice obligation and one full opportunity for a 30-month stay will attach. This ensures that, consistent with the statute, for at least one paragraph IV certification, the NDA holder or patent owner has a full 45 days to determine whether to exercise the right to sue for patent infringement

and to obtain a 30-month stay on ANDA or 505(b)(2) approval. The phrase ''one full opportunity for a 30-month stay'' used throughout this preamble means a notice of a paragraph IV certification followed by either the full 45 day period, or notice followed by the initiation of patent litigation before the 45 days expire.

Only where both the 45 days have not run and the ANDA or 505(b)(2) applicant has not been sued for patent infringement will this exception apply. If the NDA holder brings suit before the 45 days, and the ANDA or 505(b)(2) applicant then changes its application to omit any paragraph IV certifications, the court where suit is pending can determine how to proceed.

For effective enforcement of this provision of the regulations, notice of the first paragraph IV certification(s) must be given by the ANDA or 505(b)(2) applicant either: (1) When the applicant receives from us an acknowledgement that the ANDA or 505(b)(2) application is sufficiently complete to permit substantive review, or (2) at the same time that the amendment to the ANDA or 505(b)(2) application is submitted to us. These requirements are already contained in our regulations at § 314.95(b) and (d) and § 314.52(b) and (d). (These also apply to a second notice of a paragraph IV certification when the first notice did not result in a full opportunity for a 30-month stay.) The importance of ANDA and 505(b)(2) applicants providing this notice was recently reaffirmed in *TorPharm, Inc.* v. *Thompson*, Civ. No. 03–0254 (D.D.C. April 25, 2003) (appeal pending). ANDA and 505(b)(2) applicants shall submit proper documentation of notice to us as required by §§ 314.95(e) and 314.52(e).

Second, an applicant who filed a paragraph IV certification with its original ANDA or 505(b)(2) application could change its paragraph IV certification (generally to a paragraph III certification) after a patent infringement suit is filed and after the 30-month stay has commenced. Such a change could occur, for example, as a result of a court order after a finding of infringement in the patent litigation. In this circumstance, an application that previously contained a paragraph IV certification would no longer do so. If such an application is subsequently amended to add a new paragraph IV certification, the notice obligation will not be triggered for the new certification. The notice requirement and one full opportunity for 30-month stay will have been exhausted when the first patent lawsuit was filed and a 30-month stay was imposed.

The third situation could occur when an applicant withdraws an ANDA or 505(b)(2) application that contained a paragraph IV certification after it has provided notification to the NDA holder and patent owner. If an ANDA or 505(b)(2) applicant were to reactivate its withdrawn application, it might contend that the notice that it provided prior to withdrawal of the ANDA or 505(b)(2) application was the only notice that could trigger a 30-month stay, regardless of whether the 45 day period had run, whether patent infringement litigation was initiated, or whether that litigation was terminated because of withdrawal of the application.

Our pre-existing regulations prevent an applicant from using withdrawal to defeat the opportunity for one 30-month stay. Under §§ 314.52(b) and 314.95(b), the applicant is not to give notice until it receives an acknowledgement letter from us stating that its application is sufficiently complete to permit review. Any notice sent prior to receipt of such letter will not constitute the notice that creates the full opportunity for the single 30-month stay.

Once the review period begins, an application may not be withdrawn and then ''reactivated.'' If the ANDA or 505(b)(2) application is withdrawn during the review period, we ''will treat the resubmission as a new application or abbreviated application'' under § 314.100(b). If the applicant wishes to have the withdrawn ANDA or 505(b)(2) application reviewed, it must submit it as a new ANDA or 505(b)(2) application. The ''decision to withdraw the application is without prejudice to refiling'' as noted in § 314.65. However, we will treat the new ANDA or 505(b)(2) application in the same manner as any other original application. The applicant will be required to provide notice for paragraph IV certifications contained in the new ANDA or 505(b)(2) application, with the possibility of a single 30-month stay. If the new ANDA or 505(b)(2) application contains no paragraph IV certification, notice must be provided if it is later amended to include such a certification. In short, withdrawal of an ANDA or 505(b)(2) application will not defeat the opportunity for a 30-month stay of approval for the resubmitted ANDA or 505(b)(2) application.

We do not agree that § 314.94(a)(12)(viii) supports a ''relation back'' theory. The provision does provide that when an ANDA or 505(b)(2) applicant changes a certification in its application, ''the application will no longer be considered to contain the prior certification,'' but it cannot be read to suggest that the application will be considered to have contained only the changed certification retroactively to the date that the original certification was filed. If interpreted in that manner, an ANDA or 505(b)(2) applicant could amend certifications to other patents and make them paragraph IV certifications. Among other difficulties, an applicant could then argue that, by virtue of relating back, such a paragraph IV certification was the ''first'' application with a paragraph IV certification, potentially entitling the applicant to exclusivity under section 505(j)(5)(B)(iv) of the act. This theory would lead to absurd results in the application of 180-day exclusivity.

Furthermore, we note that ANDA applicants have substantial incentives to avoid manipulation of the patent certification process. The 180-day marketing exclusivity provided in section 505(j)(5)(B)(iv) of the act is a significant incentive for ANDA applicants to file legitimate paragraph IV certifications. Exclusivity as to each listed patent is available only to the first ANDA applicant filing a paragraph IV certification. Frequently, there is a race to submit the first paragraph IV certification. Consequently, given this incentive, we do not anticipate that ANDA applicants will manipulate their patent certification filings, because they could jeopardize their chances of obtaining the valuable 180-day exclusivity.

We encourage ANDA and 505(b)(2) applicants to resolve their concerns about commencing litigation quickly by providing voluntary notice to the NDA holder and patent owner as they wish. There is nothing in the final rule to prevent ANDA or 505(b)(2) applicants from providing notice on their own initiative, nothing to prevent NDA holders or patent owners from responding with patent litigation, and nothing to prevent ANDA or 505(b)(2) applicants from not marketing during the litigation. To the extent that ANDA or 505(b)(2) applicants seek resolution of outstanding patent issues before entering the market, we note that the applicant can file a declaratory judgment action (as discussed below) and enter into a stipulated preliminary injunction pursuant to which the ANDA or 505(b)(2) applicant will not enter the market during the course of the litigation. Such a stipulation, of course, must be consistent with FTC precedent and established antitrust requirements. Information on pertinent FTC consent orders may be obtained from the FTC or its Internet Web site.

The interpretation we are adopting in the final rule allows only one 30-month stay per ANDA or 505(b)(2) application;

it does not permit multiple 30-month stays. Revising the rule to impose additional 30-month stays would be contrary to our interpretation of the act and the reasons for the rulemaking. Furthermore, requiring notice and imposing a second full opportunity for an additional 30-month stay under the circumstances described would be inconsistent with our legal basis for a single 30-month stay since we permit notice and one full opportunity for a 30-month stay per ANDA or 505(b) application. Multiple 30-month stays increase the delay in approval of generic drugs and result in increased costs to consumers because the cost of individual drugs is reduced when generic drugs enter the marketplace and compete with the NDA drug.

b. *Should All Paragraph IV Certifications Be Made Public and Should the Notice Requirements Be Modified*? The proposed rule would limit when a notice of a paragraph IV certification is provided to NDA holders and patent owners but did not address the content or format of the notice. The proposed rule did not address whether or not paragraph IV certifications were subject to public disclosure. We invited comment on whether our regulations regarding the notice by ANDA and 505(b)(2) applicants to the NDA holder and patent owner could and should be amended (67 FR 65454).

(Comment 14) Several comments suggested that we should post all paragraph IV certifications on our Web site because, these comments argued, there is no basis to exempt the paragraph IV certifications from public disclosure. The comments also suggested that we disclose all paragraph IV certifications.

(Response) We decline to amend the proposed rule to make public all paragraph IV certifications or otherwise provide notice of paragraph IV certifications to NDA holders and patent owners. Under current practice, paragraph IV certifications are subject to public disclosure under the Freedom of Information Act (FOIA) and FDA's public disclosure regulations once the notice of the paragraph IV certification has been provided to the NDA holder and patent owner. Because the notice to the NDA holder or patent owner of the paragraph IV certification is considered a public disclosure after notice has been given, the certification is available under FOIA. The final rule requires notice only for the first paragraph IV certification of an ANDA or 505(b)(2) application if that notice results in a full opportunity for a 30-month stay. Notice for a subsequent paragraph IV certification will be required only if the full opportunity did not result. Only the paragraph IV certifications for which notice is required will be routinely subject to public disclosure prior to approval. All other certifications in an application would be considered confidential, commercial information. Unless the ANDA or 505(b)(2) applicant makes the subsequent certification public on its own accord, we are prohibited from any disclosure that would reveal the applicant's identity, contents of the application, or the timing of the application (see §§ 20.61(b) and 314.430). We do not believe that amending our FOIA regulations to permit the release of information typically considered confidential, commercial information, i.e. information that could cause competitive harm is appropriate, without deciding at this time that we could even do so.

Although parties are free to make paragraph IV certifications public themselves, we will continue to adhere to our pre-existing FOIA and public disclosure requirements as applicable to paragraph IV certifications. We also intend to publish on our Internet Web site, for each drug, the number of paragraph IV certifications filed to patents submitted after the effective date of this final rule, if it can be done in a manner that is consistent with FOIA. To avoid any inappropriate public identification, we will not publish the number of subsequent paragraph IV certifications if there is only one ANDA or 505(b)(2) application containing a paragraph IV certification because such publication would be tantamount to a public disclosure of that applicant's confidential, commercial information.

The NDA holder and patent owner also have other means to determine whether subsequent paragraph IV certifications have been filed. If a lawsuit is filed after notice of the paragraph IV certification, the NDA holder or patent owner can use the litigation process to discover the ANDA or 505(b)(2) applicant's certifications to subsequent patents. Furthermore, additional public information is available if we issue a tentative approval letter to the ANDA or 505(b)(2) applicant with a paragraph IV certification. These letters are publicly available before the ANDA or 505(b)(2) applicant receives an approval and note the applicable patents, patent certifications, and exclusivities affecting the timing of the approval of the ANDA or 505(b)(2) application.

We note that comments concerning public disclosure of paragraph IV certifications and the need for quick resolution of patent issues were submitted both by brand name or innovator firms and their trade associations and by generic drug firms or related interests. We believe such mutual interests will encourage the voluntary disclosure of paragraph IV certifications.

(Comment 15) Several comments responded to our request for comments on whether our regulations concerning the certifications filed by ANDA and 505(b)(2) applicants and the notice to NDA holders and patent owners could or should be modified. Most comments agreed that we had the authority to modify both the certifications and the notice. One comment suggested that we ''clarify the elements of a proper paragraph IV notification'' to ''ensure that paragraph IV notifications communicate meaningful information regarding the basis for an assertion that a listed patent is invalid or not infringed'' and that ''adequate'' information is provided. Another comment suggested that the notice provided to the NDA holder and patent owner of a paragraph IV certification should include an explanation of the relationship between the patent claims as construed by the ANDA or 505(b)(2) applicant and the drug product. Another comment said we should require the NDA holder and patent owner to identify an ''agent for service'' and require service by registered mail to ensure that the notice will reach its ''proper location within the corporation in a timely manner.''

(Response) In reviewing the current notification requirements at § 314.95(c), we do not believe that the suggested solutions for clarification or more detailed explanations would improve upon the current regulation. The current regulation requires specific information in a notice that explains in full, and in detail, the nature of the claim that the listed patent is invalid or, unenforceable or will not be infringed. Our regulations, at §§ 314.52(a) and 314.95(a), require notification by registered or certified mail, return receipt requested. Our regulations also require documentation of a receipt establishing that the notice was received by the listed NDA holder and patent owner (see § 314.52(e) and § 314.95(e)). A receipt other than a return receipt or a letter from the recipient acknowledging receipt can be provided only with advance FDA agreement.

We do not believe it would be appropriate to further limit delivery of the notice, nor do we believe it is appropriate to require ''agents for service.'' We are not persuaded that such agents would solve the comment's problem that ''notice is not reaching its

proper location within the corporation in a timely manner.'' In addition, the individual listed as the ''agent for service'' could change, resulting in confusion and delay in providing notice.

(Comment 16) Another comment suggested we require ANDA and 505(b)(2) applicants to file a new complete application for every drug product listed separately in the Orange Book rather than allow applicants to file supplements to approved applications. This comment would require new applications for each drug strength listed in the Orange Book as a separate product.

(Response) We decline to adopt the comment's suggestions. Our current policies regarding supplements to ANDA and 505(b)(2) applications allow for significant administrative efficiencies and reduced application review times. Requiring separate ANDA or 505(b)(2) applications would substantially increase costs for applicants, as well as the agency, to accommodate the burden of creating, submitting, processing, and reviewing multiple, complete applications. Our policy regarding supplemental ANDAs for multiple strengths of a drug has been a major factor in reducing ANDA review times. Before 1991 (when applicants had to submit separate ANDAs for different strengths of a drug), the median approval time for an ANDA was 33 months. Today it is approximately 18 months. A key purpose of this final rule is to help expedite the approval of generic products so that they can more quickly be introduced to the marketplace. If we adopted the suggestion, the probable effect would be to delay the introduction of generic drugs into the market because the review times would increase. Requiring multiple applications would not provide any additional value to our review of ANDA applications. Consequently, we decline to require separate applications as suggested by the comment.

c. *Should the Single 30-Month Stay Be Further Limited*?

(Comment 17) Many comments agreed with our determination that the delay in approval of ANDA or 505(b)(2) applications could be limited to one 30-month stay per application. Other comments agreed with the limitation but stated that the single 30-month limitation was or should be:

- Per drug;
- Per ANDA, for all patents submitted before any ANDA filing; or
- Limited only to patents submitted within 30 days of NDA approval.

(Response) We decline to adopt the additional limitations as suggested by the comments. The act requires a certification for each listed patent for each application filed under sections 505(b)(2) or 505(j) of the act. We construe section 505(c)(2) of the act to require submission of patent information after NDA approval, without regard to when an ANDA or 505 (b)(2) application has been filed. We decline to limit the 30-month stay resulting from a paragraph IV certification to only those patents submitted before any ANDA or 505(b)(2) filing, or those filed only within 30 days of NDA approval, or per listed drug instead of per application.

d. *Will the Application of Only One 30-Month Stay Affect Declaratory Judgment Actions Under the Act*?

(Comment 18) Several comments supported the single 30-month stay but expressed concern that limiting the notice requirement and 30-month stays to the first paragraph IV certification could affect the ability of ANDA and 505(b)(2) applicants to file a declaratory judgment action to resolve patent infringement issues. Some comments believed that in the absence of both notice to the NDA holder and patent owner and the ensuing 45-day period within which a patent infringement suit could be initiated, a declaratory judgment action could not be brought. Other comments opposed the single 30-month stay and also expressed concern about the ability to pursue a declaratory judgment action under the proposal. Some comments questioned whether a declaratory judgment action could be filed under other statutory provisions; the comments explained that the Hatch-Waxman Amendments created the act of patent infringement and, if litigation were bought ''outside'' the act, there would be no ''case or controversy'' required by those provisions. One comment cited *Cordis Corp.* v. *Medtronic, Inc.*, 835 F.2d 859, 862 (Fed. Cir. 1987), noting that ''when the generic cannot meet the subjective standard of proving a reasonable apprehension of a suit by the brand company,'' the case may be dismissed because there was no ''case or controversy.'' Another comment cited *Teva Pharmaceuticals, USA, Inc.* v. *FDA*, 182 F.3d 1003 (D.C. Cir. 1999), to claim that if no notification were received, arguably no declaratory action could be brought. Other comments suggested that limiting NDA holders to a single 30-month stay per ANDA or 505(b)(2) application would encourage the delay of litigation designed to resolve patent issues and thus would reduce ''certainty'' for ANDA applicants.

(Response) We appreciate the desire to resolve patent issues quickly, but believe the concerns expressed about the ability to pursue declaratory judgment actions are unwarranted. Section 505(j)(5)(B)(iii) of the act provides: ''Until the expiration of forty-five days from the date the notice made under paragraph (2)(B)(i) is received, no action may be brought under section 2201 of title 28, United States Code, for a declaratory judgment with respect to the patent.'' We interpret this particular section as creating an exception to the general right of a party to bring a declaratory judgment action at any time that jurisdictional requirements are satisfied under title 28, United States Code. The general rule allowing declaratory judgments under 28 U.S.C. 2201 would be applicable as long as a party can satisfy the ''case or controversy'' requirement that is necessary to file a declaratory judgment action. The exception created in section 505(j) of the act restricts the timing when a declaratory judgment action may be filed under certain limited circumstances. Under the act, if notice of a paragraph IV certification is required, no declaratory judgment action can be filed until 45 days after that notice is given to the NDA holder and patent owner. However, if no notice is required to be provided to the NDA holder and patent owner, the exception created in section 505(j) of the act no longer applies, and the general rule permitting declaratory judgments to be filed at any time under 28 U.S.C. 2201 would apply.

We also disagree with the conclusions drawn from the cases cited in the comments that, in the absence of the notice of subsequent paragraph IV certifications, there would be no case or controversy on which to base a declaratory judgment action. A case or controversy can exist where first, there is reasonable fear of a lawsuit and, second, the plaintiff has actually produced the product in question or is prepared to produce the product. (See *Cordis Corp.* v. *Medtronic, Inc.*, 835 F.2d 859 (Fed. Cir. 1987)). In *Vanguard Research, Inc.* v. *PEAT, Inc.*, 304 F.3d 1249, 1255 (Fed. Cir. 2002), the court found that fear of a lawsuit existed when the competitor was engaged in activity subject to a patent infringement charge, and the patent holder already had sued the competitor to protect its technology. The court noted that: ''[f]iling a lawsuit for patent infringement would be just another logical step in its quest to protect its technology.'' This is similar to the

situation in which an ANDA or 505(b)(2) applicant has filed an initial paragraph IV certification and the NDA holder or patent owner has filed a lawsuit to protect the patent and obtain a 30-month stay. There is little reason to doubt that an NDA holder or patent owner who had submitted a second patent to us for listing would bring another lawsuit to protect the second patent if an ANDA or 505(b)(2) applicant were to manufacture the drug, even if no notice of a subsequent paragraph IV certification was provided. In other words, the NDA holder or patent owner should have an incentive to protect the patented invention regardless of whether the ANDA or 505(b)(2) applicant provided notice.

We acknowledge that the court in *Jervis B. Webb Co.* v. *Southern Systems, Inc.*, 742 F.2d 1388 (Fed. Cir. 1984), found that a case or controversy did not exist when the plaintiff had not produced a product (a device) at the time of the declaratory judgment counterclaim. However, an ANDA or 505(b)(2) applicant is engaged in ''producing'' a product at the time the ANDA or 505(b)(2) application is filed. Although 35 U.S.C. 271(e)(1) makes it an act of non-infringement to use a patented invention for uses related to submitting an ANDA or 505(b)(2) application (such as testing and producing sample batches of drug product), 35 U.S.C. 271(e)(2) expressly makes it an act of infringement to submit an ANDA or 505(b)(2) application seeking approval of the drug product before a patent expires. This statutory provision does not require that the NDA holder or patent owner receive formal notice of a paragraph IV certification for the submission of the application to be an act of infringement. Thus, unlike the plaintiff in *Jervis B. Webb Co.* v. *Southern Systems, Inc.*, the second element of the case or controversy test would be satisfied.

In another case cited in the comments, *Teva Pharmaceuticals, USA, Inc.* v. *FDA*, 182 F.3d 1003 (D.C. Cir. 1999), the court explained that a case or controversy did not exist in the underlying declaratory judgment action. There was no reasonable apprehension of suit—the first element of the case or controversy test—because the patent owner had disavowed an intent to sue. A disavowal of the intent to sue is an unusual circumstance that we do not expect to occur in many cases. In any event, the availability of a declaratory judgment action is less important when the innovator or patent owner disavows an intent to sue because the ANDA applicant will face less risk in marketing its competing product. We are not aware of any other Hatch-Waxman patent infringement case in which a court has found no reasonable apprehension of suit.

In response to the comments arguing that a single 30-month stay would create uncertainty regarding litigation and later-submitted patents, we note that a firm's inability to predict whether it will or will not be sued for patent infringement is a matter outside the scope of this final rule. A decision by the NDA holder or patent owner on whether to file suit for patent infringement may depend on many factors. For example, litigation decisions could be affected by the strength of the underlying patent, the party's resources, licensing agreements if the patented invention is made under a license, or other factors. We also note that some patent infringement suits may be initiated after the 45 day period available to obtain a 30-month stay has expired. The act only requires the initiation of a patent infringement suit within a specific time if the NDA holder or patent owner wishes to get the benefit of a 30-month stay in the approval of an ANDA or 505(b)(2) application; the NDA holder or patent owner can bring suit at a later time, but loses the opportunity to obtain a 30-month stay of approval.

In addition, there are various types of patents which must not be submitted for listing in the Orange Book. These patents are not subject to the certification, notice, and 30-month stay provisions. The fact that such patents must not be listed does not prevent the NDA holder or patent owner from defending those patents in litigation as it deems appropriate.

e. *Is the Correct Legal Interpretation Applied to Provide Only One 30-Month Stay*?

(Comment 19) Numerous comments challenged our proposed interpretation of the act to permit only one 30-month stay per ANDA or 505(b)(2) application. Some comments advanced a legal analysis different than the one we described in the preamble to the proposal to support a single 30-month stay. The comments asserted that their legal theories were either better than ours or were the only appropriate legal arguments possible.

In contrast, other comments maintained that section 505(j)(2)(B)(iii) of the act requires that notice be provided to the NDA holder and patent owner each time a new paragraph IV certification is added to an ANDA. These comments maintained that multiple 30-month stays are clearly required if the notices result in patent litigation. Several comments contended that the plain meaning of ''include'' or ''amended to include'' is to ''contain'' or ''comprise as part of a whole,'' and that our interpretation of section 505(j)(2)(B)(iii) of the act is not reasonable. The comments also argued that our interpretation of ''include'' in this provision differs from its use elsewhere in section 505 of the act. One comment stated that the meaning of ''include'' in sections 505(j)(7)(A)(ii) and (iii) of the act cannot be reconciled with our interpretation of that term in section 505(j)(2)(B)(iii) of the act. Section 505(j)(2)(B)(iii) of the act states that ''If an application is amended to include a certification described in subparagraph (A)(vii)(IV), the notice required by clause (ii) shall be given when the amended application is submitted.'' The comment noted that section 505(j)(7)(A)(ii) of the act provides that the Secretary ''shall revise the list [Orange Book] to include each drug which has been approved . . . during the [intervening] thirty-day period'' and, when that updated drug information is recorded ''in revisions made under clause (ii), [shall] include such [patent] information for such drug.''

Several comments questioned whether the legislative history of the Hatch-Waxman Amendments supported our proposed interpretation of section 505(j)(2)(B)(iii) of the act. One comment contended that House Report language (see 67 FR 65448 at 65456) we had cited should be read as supporting multiple 30-month stays. The comments also argued that our interpretation failed to consider the importance of the final compromise that led to a 30-month, rather than 18-month, stay to ensure that patent litigation was resolved before a generic drug was approved. Finally, other comments criticized our failure to consider other language from a House Report that allegedly shows that Congress intended the availability of multiple 30-month stays. This language, found at H. Rept. 98–857, Part 1, 98th Cong., 2d Sess. at 28, states: ''In the case where the patent certification is amended in an ANDA to allege invalidity or non-infringement of a patent, the FDA may not make the approval effective within the 45 day period that an action for patent infringement may be brought.''

(Response) We agree that section 505(j)(2)(B)(iii) of the act can be read to permit multiple 30-month stays. Indeed, this has been our position since the enactment of the Hatch-Waxman Amendments. The proposal put forth a different interpretation, one that we believe is equally reasonable and more in line with the intent of the Hatch-

Waxman Amendments—to maintain a balance between the rights of the NDA holders and patent owners, and the desire to have more rapid availability of generic drugs. Our revised interpretation of section 505(j)(2)(B)(iii) of the act accomplishes two statutory objectives: (1) It closes a possible loophole that would have allowed ANDA applicants to avoid any 30-month stay and (2) it prevents multiple 30-month stays per ANDA application. A similar conclusion applies to the parallel provisions of section 505(b)(2) of the act.

We based our change in position on a reevaluation of the statutory text and concluded that the act is ambiguous on this issue of multiple 30-month stays. We note that certain other legal interpretations or theories may support a single 30-month stay, but we believe that the position we have taken in the final rule is the most appropriate.

The preamble to the proposed rule explained the rationale for our different interpretation (see 67 FR 65448 at 65454 to 65456). In brief, after reviewing the text of section 505(j)(2)(B)(i) through (iii) of the act, we believe that these provisions may be reasonably interpreted so that notice and the opportunity for a 30-month stay do not flow from all paragraph IV certifications. However, one notice of a paragraph IV certification and one full opportunity for a 30-month stay will always be required. This outcome—the opportunity for one 30-month stay during which patent rights can be litigated, but no multiple 30-month stays per ANDA or 505(b)(2) application to unreasonably delay approvals of competitor drugs—is a reasonable and balanced interpretation of the act.

We disagree with the comments that claimed that notice and 30-month stays are required only for paragraph IV certifications contained in original ANDAs because the notice provision at section 505(j)(2)(B)(ii) references only section 505(j)(2)(B)(i) of the act. This interpretation would eliminate the opportunity for a 30-month stay in any situation where an ANDA applicant waits until an amendment to submit a paragraph IV certification. As we explained in the proposed rule (see 67 FR 65448 at 65455 to 65456), section 505(j)(2)(B)(iii) of the act specifically requires ANDA applicants to give notice if they amend their applications to include their first paragraph IV certification. For these reasons, we do not interpret the act to require that only paragraph IV certifications contained in original ANDA applications will trigger the notice requirements and the possibility of a 30-month stay.

Our interpretation ensures that the NDA holder and patent owner will receive notice of at least one paragraph IV certification and have one full opportunity for a 30-month stay. However, we also disagree that every paragraph IV certification requires notice and an opportunity for a 30-month stay. We will require notice to the NDA holder and patent owner of a later paragraph IV certification if: (1) The ANDA or 505(b)(2) application did not previously contain a paragraph IV certification, but is amended to include a paragraph IV certification; or (2) a previous notice of a paragraph IV certification did not result in one full opportunity for the 30-month stay under the act.

This approach is consistent with the statutory language. By its terms, section 505(j)(2)(B)(i) of the act, and the nearly identical language applicable to 505(b)(2) applicants, requires that the ANDA applicant submitting a paragraph IV certification in its original ANDA ''include in the application'' that it will provide the required notice. Section 505(j)(2)(B)(ii) of the act sets forth the required content of the notice referred to in clause (i). Under section 505(j)(5)(B)(iii) of the act, we are prohibited from approving an application with a paragraph IV certification if an action has been brought within 45 days of the date the notice under section 505(j)(2)(B)(i) is received. The text of section 505(j)(5)(B)(iii) refers multiple times to ''the notice provided [or made] under paragraph (2)(B)(i).'' Thus, at a minimum, it cannot be said the statute clearly applies the notice requirement to all paragraph IV certifications, whether in original or amended ANDAs.

By contrast, section 505(j)(2)(B)(iii) of the act refers to amended, not original, ANDAs. It addresses the question of notice when an ANDA is amended to include a paragraph IV certification. Our interpretation eliminates the possibility that an ANDA applicant could evade any notice that could lead to a 30-month stay by omitting any paragraph IV certification in an original ANDA, and then later amending the application to include such a certification. By providing one full opportunity for the 30-month stay, we reduce the opportunity for intentional manipulation of the filing of paragraph IV certifications.

We do not agree that the act's language governing the operation of paragraph IV certifications, notice, and 30-month stays is clear and unambiguous. As the multiple interpretations advanced by the comments demonstrate, the statutory language may plausibly be read in different ways. It is certainly reasonable to interpret ''include'' as used in the act to mean ''contain.'' That is the meaning we understood the word to have when we issued the proposed rule (see 67 FR 65448 at 65455). Thus, it is a reasonable construction of the act to conclude that when an application is amended to contain a paragraph IV certification (when it did not previously contain such a certification), it is thus amended to include such a certification; and, that once an application contains such a certification, adding a new one does not amend or change the application to include or contain one, since it already contained such a certification. In any event, reliance on words in isolation is misplaced. As Judge Learned Hand observed, ''Words are not pebbles in alien juxtaposition; they have only a communal existence; and not only does the meaning of each interpenetrate the other, but all in their aggregate take their purport from the setting in which they are used * * *.'' *NLRB* v. *Federbush Co.*, 121 F.2d 954, 957 (2d Cir. 1941). Our interpretation of the 30-month stay provision is fully consistent with this principle.

We also reject the view that our interpretation of the statutory language ''amended to include'' is inconsistent with the use of the word ''include'' elsewhere in the statute. We do not agree that the use of ''include'' in section 505(j)(7)(A)(ii) and (j)(7)(A)(iii) of the act cannot be squared with our interpretation of that term in section 505(j)(2)(B)(iii) of the act. Sections 505(j)(7)(A)(ii) and (j)(7)(A)(iii) of the act, which relate to updating the Orange Book every 30 days to take into account drug approvals and patent listings, provide that the Secretary ''shall revise the list to include each drug which has been approved * * * during the [intervening] thirty-day period'' and when that updated drug information is recorded, ''in revisions made under clause (ii), [shall] include such [patent] information for such drug.'' That language requires publication of revisions to include something that was not previously contained in the Orange Book, i.e., approved drugs and patents that were not listed in the version of the Orange Book that existed immediately before the amendments were filed. The Secretary would publish nothing, under this statutory directive, if in the preceding 30 days, no new drugs were approved or patent listings filed. Similarly, when an ANDA or 505(b)(2) application is amended to include a paragraph IV certification, when no such certification is contained in the

application prior to the amendment of the application, section 505(j)(2)(B)(iii) of the act applies. But when an ANDA or 505(b)(2) application contained a paragraph IV certification prior to the amendment and one full opportunity arose for a 30-month stay, no notice obligation is triggered for subsequent paragraph IV certifications.

We do not agree with the comment that the legislative history indicates that Congress changed the 18-month stay to a 30-month stay because it intended that patent litigation be resolved before a generic application could be approved. The House Judiciary Committee rejected an ''amendment [that] would have required that either the patent expire before approval, or that there be a final decision by a Federal District Court that the patent in question was not valid'' (see H. Rept. 98–857, Part 2, 98th Cong. 2d Sess., 9 (1984)). It appears that the amendment was rejected because the effect ''would have been to substantially delay generics from getting onto the market when they seek to challenge the validity of a patent'' (*id.* at 10). Congress explicitly rejected amendments to prohibit generic entry before judicial resolution of the patent issues prior to approval, but accepted a 30-month stay period, whether or not litigation was finally resolved, because, as a practical matter, it was believed the time period would not affect when generic manufacturers would begin to market their drugs (see 130 Congressional Record H9118 (September 6, 1984) (remarks of Rep. Waxman)).

We also believe that the legislative history quoted in the comments is ambiguous at most and can be interpreted in a way that does not undercut our changed interpretation. The report states: ''In the case where the patent certification is amended in an ANDA to allege invalidity or non-infringement of a patent, the FDA may not make the approval effective within the 45 day period that an action for patent infringement may be brought.'' Although this language does not distinguish explicitly between situations when an application already contained a paragraph IV certification and those when it did not, it would not be unreasonable to interpret it to apply only when invalidity or non-infringement of a patent is alleged for the first time. Language describing when an ANDA is ''amended * * * to allege invalidity or non-infringement of a patent'' can be read in another way as ''amended to include'' a paragraph IV certification. When an ANDA or 505(b)(2) application is amended to include an allegation of invalidity or non-infringement of a listed patent for the first time, we cannot approve the application for 45 days, and notification of the paragraph IV certification will be required. For additional paragraph IV certifications, when a patent has already resulted in a paragraph IV certification and a full opportunity for a 30-month stay, no notice is required and we do not need to wait for 45 days to approve an ANDA or 505(b)(2) application if it is otherwise ready for approval.

f. *Is There a Sufficient Basis to Adopt the Change in Legal Interpretation*? In the preamble to the proposed rule, we detailed the factual basis for our decision to reevaluate our legal interpretation of the maximum number of 30-month stays per ANDA or 505(b)(2) application (see 67 FR 65448 at 65455). We noted that our impression that multiple 30-month stays were increasing was confirmed by the FTC Report. In addition, the FTC Report found that there was an increase in submission of later-issued patents, many of which ''do not appear to claim the approved drug product or an approved use of the drug'' (*id.*).

(Comment 20) Several comments questioned the factual basis for what they called our ''dramatic change in position'' and argued that the information used in the FTC Report was already known to us. Since there was no ''new information,'' the comments maintained that the facts did not provide an ''adequate'' basis for our adoption of a single 30-month stay per ANDA or 505(b)(2) application.

(Response) We disagree with the contention that our factual basis underlying our rule was inadequate. At the outset, we note that the comments proceed from a false premise to a flawed conclusion. The ''newness'' of the underlying data is not the appropriate legal standard for evaluating the reasonableness of our different interpretation. An agency must consider ''the wisdom of its policy on a continuing basis'' ''with or without a change in circumstances'' (see *Chevron, U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837, 863, 104 S. Ct. 2778, 2792 (1984); *Motor Vehicle Manufacturers Ass'n* v. *State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 57, 103 S. Ct. 2856, 2873 (1983)). Our pre-existing regulations permitting multiple 30-month stays have led to protracted delays in generic drug approvals and, therefore, need to be changed.

If ''newness'' of the underlying data were the test, the data here would satisfy it. Over the last several years, there has been an increasing number of multiple 30-month stays for a single drug product. These stays have caused significant delays in the approval of generic versions of frequently prescribed drugs. We anticipate that if we do not address the current situation, these multiple 30-month stays and resulting delays in generic drug approvals would continue to increase. There will be an increasing number of patents expiring in the next few years covering innovator drugs currently on the market. According to our records, over 500 drug patents will expire between 2003 and 2009. We have identified 26 top-selling drugs subject to patents with expiration dates between 2003 and 2005. These 26 drugs had combined 2001 retail sales exceeding $38 billion (over 25 percent of all 2001 prescription drug expenditures) and include 7 of the top 10 best selling drugs. The pressure on NDA holders and innovator companies to protect their market share and delay generic competition into the market will continue to increase. We would expect to see an increase in the conduct documented in FTC Report if our regulations remained the same.

The FTC's comprehensive and discerning analyses of the data it collected substantiated the seriousness of the problem. The FTC analyzed the relationship between patent listings and multiple 30-month stays, conducted an extensive review of various lawsuits involving multiple 30-month stays (including lawsuits in which we were not a party) and analyzed the outcome of the litigation. Although we provided some raw data to the FTC to assist its investigations (and thus that information was not ''new'' to us), we did not have all of the data that the FTC collected nor had we analyzed the data in the manner done by the FTC.

We have concluded that our regulations permitting multiple 30-month stays have led to considerable delays in the approval of generic drugs. This consequence was not intended either by Congress or by FDA. Thus, we have changed our regulations to address this problem.

B. Miscellaneous Comments

1. Do We Need Legislation to Accomplish Our Goals?

The preamble to the proposed rule did not discuss any legislative efforts to enhance the availability of generic drugs.

(Comment 21) Several comments said that legislation would be better than rulemaking or that we should support legislation. In general, the comments felt that legislation would:

- Better resolve intellectual property issues than our rule;

• Give us clear legal authority to act or be less vulnerable to judicial review; or,

• Result in timely and predictable access to generic drugs.

One comment noted that Congress had considered several bills to address 30-month stays. The comment declared that such proposed legislative action indicated both that we lacked authority to issue the rule and that new legislation was needed. Another comment suggested that we support legislation to allow only one 30-month stay and only for patents that are listed within 30 days of an NDA's initial approval.

(Response) We believe that, under our existing regulations, there have been delays in generic drugs reaching the market, as well as confusion over certain patent listing requirements. This rule is intended to help ensure that lower cost, safe and effective generic drugs become available to Americans without any inappropriate delays, while still preserving incentives to innovate. These changes can be achieved through rulemaking, using our existing legal authority. We cannot predict whether, if at all, legislation addressing these issues will be enacted. The possibility that there could be legislation to address problems associated with 30-month stays and generic drug approvals cannot, and should not, preclude us from using our existing authority to address these problems. We also note that those comments favoring legislative solutions over regulatory ones apparently assume that legislative changes would necessarily lead to less litigation than a rule. Based on our past experience in defending statutory interpretations, we question whether such a presumption is appropriate here. We recognize that a regulation may not always be a perfect solution due to limits on our statutory authority, but that recognition does not mean that we cannot use our existing legal authority to engage in rulemaking to improve our regulatory approach.

Additionally, we disagree with the comments that claimed we lack authority to issue the rule. The preamble to the proposed rule discussed our legal authority (see 67 FR 65448 at 65457). We will not repeat that discussion here. The fact that Congress has considered, or is currently considering, bills on the 30-month stay issue does not preclude us from exercising our existing authority, nor demonstrate that we presently lack that authority. As the Supreme Court has explained:

> We have stated * * * that failed legislative proposals are a particularly dangerous ground on which to rest an interpretation of a prior statute. Congressional inaction lacks persuasive significance because several equally tenable inferences may be drawn from such inaction, including the inference that existing legislation already incorporated the offered change.

(See *Central Bank of Denver* v. *First Interstate Bank of Denver*, 511 U.S. 164, 187 (1994).)

(Citations and internal quotation marks omitted.)

Although it would be both inappropriate and premature for us to take a position on any legislative concept without seeing the details of any specific proposed or draft legislation, we are always willing to work with Congress. Until then, we will not take a position on legislation to allow only one 30-month stay for patents filed within 30 days after NDA approval.

2. Will the Different Interpretation Affect Existing Exclusivities?

We stated in the preamble to the proposed rule that the implementation of the final rule would not affect an ANDA's eligibility for 180-day exclusivity under 505(j)(5)(B)(iv) of the act (see 67 FR 65448 at 65457).

(Comment 22) Several comments addressed different aspects of the 180-day and 3 year exclusivity provisions of the Hatch-Waxman Amendments. The comments offered suggestions on changing the exclusivity trigger, requiring the forfeit of the exclusivity if parties agree to delay marketing and expressed concerns about the potential increase in the availability of 180-day exclusivity if we allow additional patents to be filed.

(Response) We appreciate the complexities of the various exclusivities provided by the act. As we noted in the proposed rule, eligibility for 180-day exclusivity will follow the same general principles as before implementation of this final rule. The first ANDA applicant to file a substantially complete ANDA, or supplement, containing a paragraph IV certification to a listed patent will be eligible for exclusivity as to that patent under section 505(j)(5)(B)(iv) of the act. For a paragraph IV certification to be effective for exclusivity purposes, when notice is required, notice must be given as described in the response to comment 13 of section II.A of this document. However, when notice is not required, a paragraph IV certification will be effective for exclusivity purposes without notice. We understand that each patent listed in the Orange Book may form the basis for a claim to 180-day exclusivity. Thus an increase or decrease in listed patents as a result of this final rule could affect the number of exclusivity periods. Other suggestions made in the comments are beyond the scope of the final rule. We are not altering our interpretation of exclusivity in the final rule.

3. Should the Provisions of the Final Rule Be Severable?

The proposed rule did not address whether each provision should be considered independent of other provisions and, thus, severable if any provision were determined to be invalid.

(Comment 23) Although there were no comments that directly addressed severability, one comment suggested that the limitation on multiple 30-months stays was unnecessary because the revised patent listing provisions would prevent improper patents from being submitted for listing in the Orange Book.

(Response) Although we agree that the changes to the patent submission and listing provisions and the information required on the declaration forms will help ensure that improper patents are not submitted for listing, we also believe that eliminating multiple 30-month stays will help maintain the balance intended by the Hatch-Waxman Amendments and is equally important to the final rule. Each of the final rule provisions reinforces interrelated goals. Clarifying that certain patents may not be submitted for listing should lead to the submission of fewer improper patents. Requiring additional patent declaration information from NDA applicants or holders or patent owners also should help ensure that only eligible patents are submitted. Eliminating the opportunity for multiple 30-month stays also should reduce incentives to submit improper patents.

Based on our past experience we acknowledge that the provisions of this final rule will neither completely resolve all issues governing patent submission, nor will they eliminate attempts to manipulate the final rule for market advantage. We also believe that each provision will reduce the opportunities for manipulation and, thus, is independently justified and worthwhile. However, we believe each provision stands on its own as a legal and practical matter.

From the comments we have received to the proposed rule, we believe there is a possibility that we will be challenged on various portions of the final rule. We expect we will prevail in any such challenge, as the final rule and each of its provisions is legally sound. If, however, a court should conclude that any one or more provisions of the final

rule is invalid, we wish to emphasize our intent that the remaining provisions of the final rule be permitted to take effect.

4. Implementation and Effective Date

The preamble to the proposed rule described how a final rule would be applied to pending applications (see 67 FR 65448 at 65457) 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 with 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 regulations, 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.

We invited comment on how a final rule should be implemented.

(Comment 24) Several comments suggested alternative effective dates including the following:

• Apply the final rule to all ANDAs filed before the effective date of the final rule and cancel any existing multiple 30-month stays;

• Apply the final rule retroactively to all current NDA holders by requiring all NDA holders to be subject to only one 30-month stay and apply the declaration provisions to require all current NDA holders or patent owners to file a new declaration and certification for already listed patents using the declaration statement in the proposal;

• Apply the new declaration requirements retroactively to require the new information on patents currently listed in the Orange Book; if the propriety of a patent listed in Orange Book for a current NDA holder or patent owner is questioned, the NDA holder or patent owner must file a new declaration or FDA should delist the patent.

In contrast, other comments supported the implementation plan as proposed.

(Response) We will implement the final rule on a prospective basis, as we stated in the proposed rule. The fact that we made our intent public in a proposed rule and the time lag between when the rule was proposed and when this final rule is effective provides sufficient time for most parties to adjust their practices and expectations, or to take other steps to suit their business practices.

We do delay the implementation date for submission of information concerning a patent claiming a polymorph that is the active ingredient of the drug product described in the approved NDA. We provide a longer period of implementation to accommodate the tests required to establish that the drug product containing the polymorph will perform the same as the drug product described in the NDA. This test data must exist when a polymorph patent is submitted to us. We recognize that the testing necessary to obtain the data for submission of polymorph patents claiming the active ingredient of the product described in the NDA may take at least 6 months to complete. There will be NDA applicants and holders and patent owners who have not already conducted testing. The 6 months will provide time for NDA applicants and holders and patent owners with patents pending at the PTO to conduct the tests needed to produce the data required for the declaration statement in time to submit any newly issued patent within 30 days of issuance.

We also decline to apply the final rule retroactively. If we canceled all multiple 30-month stays currently applicable to ANDAs and 505(b)(2) applications or applied the declaration requirements to already submitted patents for existing NDAs, we would be applying the provisions retroactively. As we noted in the proposal (67 FR 65448 at 65457): ''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.'' As a general matter, a statutory grant of legislative rulemaking does not encompass the power to implement such regulations on a retroactive basis in the absence of express language granting such power (see *Bowen* v. *Georgetown University Hospital*, 488 U.S. 204, 208–09 (1988)). There is no question that this rule ''changes the legal landscape'' (see *National Mining Ass'n* v. *Department of Labor*, 292 F.3d 849, 858 (D.C. Cir. 2002)). Applying this rule retroactively would subject us to potential legal challenge. Thus, adopting these suggestions would lead to even greater uncertainty as to the applicability of the provisions.

After further consideration, however, we believe that the proposed rule's implementation plan will not fully effect our intent to implement the provisions only prospectively. Accordingly, as described in section IV of this document, we have clarified our implementation plan to ensure prospective application of the final rule. Nevertheless, patent owners may voluntarily complete, and NDA holders may voluntarily complete and submit, new patent declarations, using FDA Forms 3542 and 3542a, for patents not subject to the final rule and currently listed in the Orange Book. This course is particularly advisable for method-of-use patents, in light of the *Purepac* decision and concerns about implementation of section 505(j)(2)(A)(viii) of the act. Such voluntary submission of new patent declarations will not bring patents within the scope of the final rule with respect to notice and 30-month stays.

III. Description of the Final Rule

A. Section 314.53(b)—What Patents Must Be Submitted?

1. Which Patents Would the Final Rule Require To Be Submitted?

Section 314.53(b) describes the patents for which information must be submitted. The final rule states, in relevant part, that information must be submitted on the required declaration forms for each patent that claims the drug or a method of using the drug that is the subject of the NDA 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. The patents include patents that claim:

- The drug substance (active ingredient),
- The drug product (formulation and composition), and
- A method of use.

Those patents that claim a different polymorphic form of the drug substance that is the active ingredient described in the NDA must be submitted if the applicant has test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. The drug product (formulation and composition) patents submitted must claim the specific drug product described in the pending or approved NDA. For patents that claim a method of use, the NDA applicant or holder must submit only those patents that claim indications or other conditions of use that are the subject of a pending or approved application. Each pending or approved method of use and related patent claim must be described.

2. What Patents Must Not Be Submitted?

Section 314.53(b), as finalized, states that information on patents claiming packaging, patents claiming metabolites, and patents claiming intermediates must not be submitted. Process patents also must not be submitted. The final rule clarifies that the prohibition on submission of packaging patents does not apply to patents that claim the drug product as defined in § 314.3. If a patent claims the finished dosage form of the drug product, it must be submitted for listing.

B. Section 314.53(c)—What Does the Patent Declaration Say?

Section 314.53(c)(1) describes the general requirements for submission of patent information and the conditions for acceptance of the patent information. Section 314.53(c)(2)(i) requires a person submitting an NDA, an amendment, or a supplement, to submit an original signed declaration form as part of its submission of patent information. The appropriate declaration form must be used for submitting patent information. The information required to be submitted is described. Each form seeks specific patent information and requires a signed attestation from the NDA applicant or holder or patent owner that the information is accurate and complies with the requirements of the regulations.

Section 314.53(c)(2)(ii) requires that the NDA holder submit a declaration form with information relating to the approved NDA and additional information on use codes within 30 days of NDA approval. The information required to be submitted is described. Each form includes specific patent information and requires a signed attestation from the NDA holder or patent owner that the information is accurate and complies with the requirements of the regulations. This section also requires submission of information on patents submitted for listing after NDA approval. This declaration form is the only declaration form that we will rely on to determine whether a patent is eligible for listing based on the patent information submitted.

C. Section 314.53(c)(3)—What Is Required to Be Filed If There Are No Relevant Patents?

The final rule modifies the statement used to describe the fact that the NDA applicant or holder believes there are no relevant patents to be submitted. The language is changed to conform to the descriptions used for drug substance (active ingredient), drug product (formulation and composition) and method of use to those used in the other regulatory provisions.

D. Sections 314.95(a) and 314.52(a)—When Are Notice and Certification Required?

The final rule modifies §§ 314.95(a) and 314.52(a) to state that, if an ANDA or 505(b)(2) application is amended to include a paragraph IV certification, notice must be provided to the NDA holder and patent owner only if the application did not already contain a paragraph IV certification or there was not a full opportunity for a 30-month stay. If an ANDA or 505(b)(2) applicant changes its paragraph IV certification before the 45-day period after notice to the NDA holder and patent owner has expired, and the NDA holder or patent owner has not initiated patent litigation, such paragraph IV certification and related notice are not considered to have satisfied the requirement of providing one notice of a paragraph IV certification and a full opportunity for a 30-month stay.

IV. Implementation

The final rule will be effective on August 18, 2003.

- Patent information submitted to us (FDA) before the effective date will be subject to our pre-existing regulations governing patent submission, declarations, certifications, notice and availability of 30-month stays;
- Patent information submitted to us on or after the effective date will be subject to the final rule's provisions governing patent submission, accompanying declarations, certifications, notice and availability of 30-month stays;
- Patent information submitted to us on a newly applicable claim, even if the patent was previously submitted to us, will be subject to the final rule's provisions.

The final rule will have a compliance date of December 18, 2003, for patent information submitted to us on patents claiming a polymorph of the same active ingredient of the product described in the NDA.

As a result, within a single same approved or pending NDA, some patents may be subject to our pre-existing regulations while other patents may be subject to the final rule. The date on which the patent information was submitted to us will determine which set of regulations applies.

We believe that the effective dates will provide adequate time for the NDA applicants, NDA holders, and patent owners to adjust their business practices. The patent information required for submission is information readily available to the NDA applicants and holders and patent owners.

We have delayed the implementation date for patent information to be submitted to us on patents claiming a polymorph that is the active ingredient of the drug product described in the approved NDA. NDA applicants and holders and patent owners with patents pending at the PTO will have additional time (i.e., until 6 months after the date of publication in the **Federal Register**) to conduct the tests needed to produce the data required for the declaration statement in time to submit any newly issued patent within 30 days of issuance.

V. Legal Authority

Our principal legal authority for the final rule is section 505 of the act, in

conjunction with our general rulemaking authority in section 701(a) (21 U.S.C. 371) of the act. Section 505(b) and (c) of the act describes the contents of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements. Section 505(j) of the act describes the contents of an ANDA, including patent certification requirements. Sections 505(b)(2)(A) and 505(j)(2)(A)(vii) of the act, respectively, require patent certifications, while sections 505(b)(3) and 505(j)(2)(B) of the act require those applicants who have made a paragraph IV certification to provide notice to the NDA holder and patent owner.

The final rule clarifies the types of patents which NDA applicants and NDA holders must and must not submit to FDA for listing in the Orange Book. It also requires a more detailed patent declaration from NDA applicants and NDA holders or patent owners using declaration forms. The specific legal authority for each provision is set forth in the preamble discussion accompanying it.

For ANDA and 505(b)(2) applicants, the final rule reduces the number of notifications sent to patent owners and NDA holders. The specific legal authority for this action is set forth in the preamble discussion of our changed interpretation.

VI. Environmental Impact

We have 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.

VII. Executive Order 13132: Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that this final rule does not contain policies that have substantial direct effects on the States, on the relationship between the 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 final rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VIII. Paperwork Reduction Act of 1995

This final 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.

Title: Applications for FDA Approval to Market a New Drug: Patent Submission and 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 final rule clarifies the types of patent information that must and must not be submitted to FDA as part of an NDA, an amendment or supplement. The final rule also requires persons submitting an NDA, amendment or supplement, or submitting information on a patent after NDA approval, to make a detailed patent declaration using required FDA declaration forms. The final rule permits the possibility of only one 30-month stay per each ANDA or 505(b)(2) application's approval date in the event of patent infringement litigation because the final rule does not require ANDA or 505(b)(2) applicants to provide a notice of certification of invalidity or noninfringement of a patent if the application already contains such a certification or if a full opportunity for a 30-month stay resulted after such notice.

Description of Respondents: Persons submitting an NDA, amendment or supplement, or submitting information on a patent after NDA approval, and persons submitting an ANDA or 505(b)(2) application containing a patent certification of invalidity or noninfringement of a 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) (citing 21 CFR 314.53) FDA Forms 3542 and 3542a	107	2.8	296	1,684	498,464
314.50(i)(1)(i) and 314.94(a)(12)	74	1.5	111	4	444
314.52(a)(3) and 314.95(a)(3)	74	1.01	74	12	897
Total					499,805

[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. For the years 1998 to 2002, the annual number of original applications we have received containing a paragraph IV certification has been 61, 58, 79, 90, and 82, respectively. The annual average is 74 ((61 certifications + 58 certifications +79 certifications + 90 certifications + 82 certifications) / 5 years = 74 certifications / year). Because the final rule requires notice of a paragraph IV certification filed in the original ANDA or 505(b)(2) application or when the application is amended to include a paragraph IV certification or when such notice did not provide a full opportunity for a 30-month stay, this would mean that these applicants would provide one notice to NDA holders and patent owners, and, in rare instances, a second notice. We increase the frequency of response to account for these rare second notices. There may still be multiple certifications made by ANDA or 505(b)(2) applicants which will not require notice. In previous estimates, we have combined the information collection burden for both the notice and certification. For purposes of the final rule, we assume that the certification information collection burden is 4 hours and the information collection burden for the notice is 12 hours. We also account for the multiple number of certifications that may have to be provided by an ANDA or 505(b)(2) applicant. Under pre-existing regulations, we have had

NDA holders submit two or more patents for a single NDA. While this may continue to occur, we believe that this final rule may reduce the number of patents submitted for listing because we have clarified the type of patents that must be submitted. The number of patents submitted could increase because we allow polymorph patents to be submitted or it could decrease if no test data exist to demonstrate that a drug product containing the polymorph will perform the same as the drug product described in the NDA. We, thus, estimate the number of annual certifications at 1.5 x 74 (the number of original certifications). Thus, the information collection burden for §§ 314.50(i)(1)(i) and 314.94(a)(12) (certifications) would be 444 hours (74 respondents x 1.5 response per respondent x 4 hours per response = 444 hours). The information burden for §§ 314.52(a)(3) and 314.95(a)(3) (notices) would be 897 hours (74 respondents x 1.01 response per respondent x 12 hours per response).

To estimate the number of enhanced patent declarations that will be submitted annually, we referred to historical data on patent submissions. For the years 1998 to 2002, the numbers of patents submitted to us were 159, 205, 321, 280, and 268 respectively, for an annual average of 246.6 ((159 patents +205 patents +321 patents+280 patents+268 patents) / 5 years = 247 patents / year). Because many of these individual patents are included in multiple NDA submissions, there could be multiple declarations for a single patent. From our review of submissions, we believe the number of duplicate patent listings to be 20 percent of the number of unique patents. Therefore, we estimate 49.2 (246.6 patents x 20 percent) patent declarations will be multiple listings, and there will be 296 (247 declarations + 49 declarations = 296 declarations) total annual patent declarations. As we received 115 and 99 NDAs in 2000 and 2001, respectively, we assume there will be 107 ((115 applications + 99 applications) / 2 years = 80 applications / year) instances where an NDA holder would be affected by the patent declaration requirements and that each of these holders would, on average, submit 2.8 (296 declarations / 107 instances = 2.8 declarations per instance) on FDA Forms 3542 or 3542a.

However, § 314.53(b) and (c) have different impacts on the hours per response. On the one hand, § 314.53(b) might decrease the reporting burden because it would specify certain patents that must not be submitted, and thus NDA applicants and holders and patent owners will not submit information on those patents. On the other hand, § 314.53(b) will require NDA applicants and holders or patent owners to submit patent information on different forms of the active ingredient described in the NDA, and this could result in more patent information being submitted or less patent information if test data do not exist to demonstrate that a drug product containing the polymorph will perform the same as the drug product described in the NDA. 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 change in patent information alone.

In contrast, § 314.53(c) makes the patent declaration more detailed. The change in the declaration will increase the burden hours per response under § 314.50(h) (the provision under which we covered patent declarations described in § 314.53(c)) because respondents will 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 estimate that the information required to be submitted on the patent declaration forms, FDA Forms 3542 or 3542a, will result in an additional information collection burden of 18 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) (see 66 FR 29143 at 29146, May 29, 2001). We are unable to determine how many of the 1,666 hours were devoted to patent declarations, so, in this table, we simply add 18 hours to the 1,666 hour estimate for § 314.50(a) through (f), (h), and (k), resulting in a burden hour estimate of 1,684 hours (1,666 hours + 18 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)(citing § 314.53) will increase from the estimate we made in the proposed rule of 209,560 hours to 498,464 hours (296 annual responses x 1,684 hours per response = 498,464 hours).

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Analysis of Economic Effects

We have examined the impacts of the 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 the Small Business Regulatory Flexibility Act (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 expenditures 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 rule, and have determined that the rule is consistent with the principles set forth in the Executive Order and in these statutes.

The final rule is a significant regulatory action as defined by the Executive Order. With respect to the Regulatory Flexibility Act, we certify that this final rule is not expected to have a significant impact on a substantial number of small entities. This regulatory action is also a major rule under the Congressional Review Act. The discussion of costs and benefits is consistent with the requirements of the UMRA.

A. Summary

The economic impacts arise from a variety of effects of this rule. The primary effect is the elimination of multiple 30-month stays, which (as explained earlier) will result in earlier market entry by generic drug manufacturers without appreciable effects on pharmaceutical innovation. Earlier generic competition will result in gains for two groups. It will reduce pharmaceutical prices to consumers and increase net revenues of generic drug manufacturers. Earlier competition also

will result in a revenue loss for innovator drug companies, which will be offset slightly by a reduction in associated costs. We believe that the rule will also reduce legal fees associated with disputed patents, although we are unable to provide quantitative estimates of this effect. In addition, innovator drug companies will face a burden of completing revised patent declaration forms. Finally, those NDA holders wishing to submit patents claiming different polymorphs of the active ingredient described in the NDA will need to have test data demonstrating ''sameness.'' Table 2 below provides a summary of our estimates of these effects and overall net benefits. The benefits and costs are annualized at a 7-percent discount rate over 10 years. We have chosen this time period because the Centers for Medicare and Medicaid Services (CMS), the source of the most reliable pharmaceutical expenditure estimates, projects these expenditures only for the next 10 years. We expect that this rule will generate substantial net benefits beyond this time period.

TABLE 2.—ECONOMIC EFFECTS OF THE RULE[1]

Effects	Amount per year (millions of dollars)
Gains	
•Savings to consumers	3,290
• Net revenues to generic manufactures	1,810
•Reduced legal costs	Not quantified
Losses	
• Revenue loss to innovator firms (net of associated costs)	4,870
• Costs of patent declarations and data to support polymorph patent submissions	<10
Net Benefits	220

[1] Gains and Losses include impacts of an economic transfer in addition to changes in resource costs.

These estimates are derived using methods and data similar to those described at more length in the preamble to the proposed rule published in the **Federal Register** on October 24, 2002 (*see* 67 FR 65448 at 65459 to 65464). In that analysis, we found that the increase in revenues to generic drug manufacturers would be $19.117 billion over 10 years, or $1.8 billion per year if annualized assuming a 7-percent discount rate. The benefit to consumers would be $34.822 billion over 10 years or an annualized $3.3 billion. We found that the reduction in revenues to innovator firms would be mitigated somewhat by the reduction in marketing expenses and that the cost would be $51.508 billion over ten years, or an annualized $4.9 billion. The 10-year net benefit is $2.356 billion, and the annualized net benefit is approximately $220 million.

With respect to the changes in market shares, the gains to consumers and generics equal the losses to innovators. An uncertainty estimate on the cost side would equal the uncertainty on the benefit side of such a transfer and would not affect our projection of net benefits. Our projection of net benefits is driven by our estimate of support costs. The primary economic impact of this action is a transfer from innovator drug firms to consumers and generic drug firms. But as innovator drug firms face a decline in revenues, they will save substantial resources used to support their products. These support costs, which include marketing, advertising, and administration, outweigh the costs associated with polymorph testing and completing the revised declaration, so the rule is a net benefit. These support costs are based on a point estimate provided by literature that does not customarily provide confidence intervals. We cannot, therefore, provide confidence intervals about our net benefit estimate, but believe the uncertainty to be small, relative to the projected net benefit.

We received no comment on the analysis published with the proposal. We continue to believe these estimates to be reasonable and include them in the final rule. This final rule, however, contains provisions that differ from what was in the proposed rule. To account for these provisions, we have changed our analysis of the burden of providing the information required for completing the patent declaration and we assess the impact of the requirement that NDA applicants or holders or patent owners submitting patents claiming different polymorphs of the active ingredient described in the NDA. In all other major respects, however, our analysis is unchanged from the proposal, so we do not repeat here some parts of our analysis that were described in detail in the proposal (see 67 FR 65448 at 65459 to 65464).

B. Benefits of the Regulation

We have identified two principal effects from the elimination of 30-month stays. These effects are impacts associated with parties gaining in economic transfer. Generic drug manufacturers gain the market share lost by innovators. Generic revenues, therefore, would be expected to increase. Also, to the extent that these generic drugs are less expensive than innovator drugs, consumers will benefit from saving money as a result of earlier access. Our model, as described in the proposed rule (see 67 FR 65448 at 65460 to 65462), estimates costs and benefits to consumers and innovators and generic drug firms for the first year the rule would be in effect. The projected changes in market shares and prices in the model are based on studies published in the economic literature and by FDA. We then escalate the 1-year estimates by the CMS—projected annual percentage increases in prescription drug expenditures to obtain estimates for 10 years. This 10-year stream is then annualized at a 7-percent discount rate to obtain the annualized estimate.

1. Gains to Consumers

Generic drugs are cheaper than their innovator counterparts. As a generic drug gains market share and its price falls, consumers save more money. The elimination of multiple 30-month stays per ANDA and 505(b)(2) applications and earlier market entry by generic drugs will reduce consumer expenditures on pharmaceuticals. We estimate that the 1-year savings to consumers are projected to be $2.040 billion. We use the CMS pharmaceutical expenditure projections to escalate the base year figure results in a 10-year consumer savings estimate of $34.822 billion for the final rule. Our annualized benefit using a 7-percent discount rate is $3.288 billion, the same as the proposed rule.

2. Gains to the Generic Drug Industry

Innovator market share erosion is accompanied by a gain in generic market share. We estimate the 1-year increase in revenues to be $1.120 billion. Escalating this impact by the annual increases in pharmaceutical expenditures yields a 10-year revenue gain of $19.117 billion. Our annualized impact using a 7-percent discount rate is $1.805 billion. These estimates are the same as in the proposed rule.

3. Benefits Not Quantified

Many important benefits associated with this final rule are difficult to quantify. The benefits to consumers from lower prices also involve favorable secondary benefits from improved access to less expensive drugs. While the economic literature indicates generic competition does not lead to significant overall increases in the quantity of drugs demanded, we nevertheless recognize this rule has favorable distributional effects for consumers who otherwise may not have been able to afford some medications. Such a benefit is consistent with the objective of improving access to affordable quality healthcare. Consumers with better access to affordable safe and effective therapies are healthier and enjoy a higher quality of life.

By addressing multiple 30-month stays, this final rule is removing a barrier to entry for generic drug firms. In principle, the removal of a barrier to entry would imply an increase in economic efficiency. The existing economic literature, however, indicates no significant increase in the quantity of drugs demanded with generic entry, implying no gain in efficiency from the removal of the barrier to entry. Thus, we do not quantify any efficiency gains in our analysis. Nevertheless, this rule encourages more and earlier market entry by generic drug firms and may impact consumption in a way not captured by the economic literature. To that extent, we believe this rule has the potential to increase economic efficiency.

The costs of allocating legal resources to defend patent protections are substantial. We do not know the extent to which this final rule will reduce such costs, but by eliminating multiple 30-month stays per ANDA and 505(b)(2) application, we are reducing the number of instances where innovator and generic drug firms would engage in such litigation. Moreover, we believe that this rule will reduce litigation because it clarifies which patents must and must not be submitted and reduces incentives for submitting patents that may ultimately be found invalid. It logically follows that the reduction in resources devoted to litigation would result in savings to both innovator and generic drug firms.

This final rule reduces the level of uncertainty associated with drug marketing decisions. For example, the final rule diminishes incentives associated with submitting later-issued patents late in the patent life or exclusivity period of the product described in the NDA. Increasing the predictability of the generic drug entry process reduces product introduction costs faced by generic drug firms. In the final rule, we are also addressing a source of confusion over the submission of polymorph patents for listing in the Orange Book. We believe that a more predictable business environment benefits both innovator and generic drug firms.

Another important benefit of the final rule involves the balance between rewarding innovation and the availability of less expensive drugs. In striking this balance, we do not believe that the Hatch-Waxman Amendments intended to create the potential for NDA holders to obtain multiple 30-month stays to unduly delay generic competitors. We believe this balance to be important, yet find the value difficult to quantify. Nevertheless, in addressing the issue of multiple 30-month stays, we believe this action has the very valuable benefit of preserving the balance struck in the Hatch-Waxman Amendments.

4. Total Benefits of the Regulation

The total quantified benefits of this final rule include the gains in generic drug manufacturer revenues and consumer savings from earlier access to less expensive pharmaceuticals. These quantified gains to consumers and generic drug companies are the result of an economic transfer. The 1-year benefits to generic drug manufacturers and consumers are $1.119 billion and $2.040 billion, respectively. Escalating these base year costs over 10 years yields generic drug manufacturer revenue gains of $19.117 billion and consumer savings of $34.822 billion, for a total of $53.940 billion. The 10-year annualized benefits, using a 7-percent discount rate, are $1.805 billion for generic drug manufacturers and $3.288 billion for consumers, for a total of $5.093 billion.

C. Costs of the Regulation

In the proposed rule, we identified two sources of costs. Innovators lose revenues from earlier generic competition and innovators must complete patent declarations. The loss in revenues to innovator drug companies is part of an economic transfer, but is included in this analysis with the resource costs associated with this action. We summarize the revenue loss and we assess the costs associated with the declaration requirement. In addition, we estimate the burden to industry from the requirement that, for submission of patents claiming different polymorphs of the active ingredient described in the NDA, there must be test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.

In the proposed rule, we addressed potential concerns about the effect this action may have on innovation. After considering potential impacts, we concluded that any negative effect would be minimal. As discussed in the proposed rule, 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. According to the FTC report, most of the court rulings examined by the FTC, which involved a subsequent 30-month stay, found the underlying patent to be either invalid or not infringed. Extending market exclusivity through multiple stays is a strategy that has become popular in the last few years and is not a longstanding 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 be associated with increases in spending on research, these increases do not necessarily improve social welfare (see 67 FR 65460). We received no comment on our assessment of the impact on innovation and continue to believe it to be reasonable.

1. Innovator Revenue Loss

As discussed in the analysis of impacts in the proposed rule, the elimination of multiple 30-month stays per ANDA or 505(b)(2) application allows generic drugs to enter the market earlier. Upon entry, generic versions of an innovator drug gradually lower their prices and take market share from the innovator. With the loss of market share, innovator revenues are lower than they would be had the innovator been allowed to use multiple 30-month stays to delay generic entry. In the analysis in the proposed rule, we used data from instances where generics had been blocked with multiple 30-month stays and calculated the impact of a typical

drug being blocked for a typical period of time. We estimated the 1-year loss in innovator revenues to be $3.160 billion. As discussed in the proposed rule, we believe that the negative impact on innovators from earlier generic competition will be mitigated somewhat by a reduction in required innovators' costs. With earlier generic competition, innovators will reduce marketing expenses. In the proposed rule, we estimated the 1-year reduction in support costs to be approximately $142 million. For the final rule, we estimate that the 1-year loss in revenues, after adjusting for the reduction in support costs, is $3.017 billion, the same as in the proposed rule.

2. Declaration Costs

In the proposed rule, we used earlier information collection data to estimate there will be 124 annual patent declarations by innovator firms. We now believe that the number of patents submitted to us each year would better estimate the annual number of patent declarations. For the years 1998 to 2002, the numbers of patents submitted to us were 159, 205, 321, 280, and 268 respectively, for an annual average of 246. We understand that many of these individual patents are included in multiple NDA submissions, so there could be multiple declarations for a single patent and this method could underestimate the number of declarations. From our review of submissions, we believe the number of duplicate patent listings to be 20 percent of the number of unique patents. Therefore, we estimate 49.2 (246.6 x 20 percent) patent declarations will be multiple listings, and there will be 295.8 (246.6 + 49.2) annual patent declarations. We have created patent declaration forms to make the submission of patent information less burdensome. The two forms, for filing with an NDA submission and upon or after NDA approval, will contain more information, but we have simplified the format to make these easier to complete. In simplifying the forms, we believe our initial estimate of 24 additional hours per declaration to complete these forms likely overstates the actual burden. To account for the simplification of the declaration process, we have lowered the expected time required to complete a patent declaration to 18 hours.

A regulatory affairs specialist could perform the tasks associated with this process. Based on the total average hourly compensation of $55.14[2] the estimated cost would be $992 ($55.14 per hour x 18 hours) per event. The burden on individual firms would depend on the number of declarations they submit. We estimate that the 1-year burden for submitting patent declaration forms is $293,000 ($992 per event x 295.8 events).

3. Cost of Submitting Polymorph Patents

We are requiring the submission of patent information for patents that claim different polymorphs of the active ingredient described in the NDA. NDA holders will now be able to submit these polymorph patents for listing in the Orange Book, as long as they have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.

We cannot make a precise estimate of the impact of these requirements, as costs can vary substantially depending on the substance being tested, the number of subjects required, the cost of raw materials, and other factors. As part of an unrelated study in 1998, we commissioned a contractor, Eastern Research Group (ERG) to estimate the cost of bioequivalence testing. We believe the burden of demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA to be similar to that of demonstrating bioequivalence. Our estimates include both the cost of manufacturing the batch and the cost of conducting the bioequivalence testing. ERG found the cost of performing such testing to be between $70,000 and $750,000.[3] We believe the cost of showing ''sameness'' to be at the higher end of this range, and estimate the burden to be between $500,000 and $750,000. The midpoint of this estimate is $625,000. (We did not adjust the ERG estimates for inflation.)

We believe a firm's decision to submit a polymorph patent for listing will depend on whether the expected benefits to the firm from listing exceed the costs of showing ''sameness.'' We recognize that potential benefits from listing polymorph patents may be reduced by the elimination in the final rule of multiple 30-month stays in approval of ANDA or 505(b)(2) applications. Thus, the cost of demonstrating ''sameness'' would deter submitting patents for listing with expected values less than approximately $625,000. We believe the typical value of a deterred polymorph patent to be substantially less than the cost of submission of the patent for listing, as many of the patents have little value without the ability to delay generic entry through multiple 30-month stays. For this analysis, we assume such low value patents to be worth approximately 20 percent of the cost of showing ''sameness,'' or $125,000.

We believe the annual number of polymorph patents that will be submitted for listing to be small, but we do not know with certainty. We reviewed a publicly available listing of NDAs in which an outside party had identified patents it judged to be polymorph patents. Of the 105 NDAs in the sample, there were 13 polymorph patents. Applying that same ratio to the 107 expected NDAs per year, we estimate 13.2 (107 x 13 / 105) potential polymorph patents to be submitted for listing per year. We assume that a polymorph patent will have a high potential value (greater than $625,000—the midpoint of the testing cost estimates) and be submitted, or will have a low potential value ($125,000) and not be submitted. With the elimination of multiple 30-month stays per ANDA or 505(b)(2) application, we believe the number of high-value polymorph patents to be a subset of the number of total polymorph patents, and assume three-fourths of the potential patents will not be submitted for listing. Thus, we assume 3.3 (13.2 potential patents x 0.25 likelihood of being high value) patents will be submitted for listing at a 1-year cost of $2.06 million (3.3 patents x $625,000 cost per patent). Likewise, we assume 9.9 (13.2 potential patents x 0.75 likelihood of being low value) patents will not be submitted each year. We estimate the 1-year cost from the inability to submit these patents for listing to be $1.24 million (9.9 patents x $125,000 value of low-value patent) and the 1-year burden associated with the test data demonstrating ''sameness'' for polymorph patents to be submitted for listing is estimated to be $3.3 million ($2.06 million + $1.24 million).

4. Total Costs of the Regulation

The total costs of the final rule include the lost revenues to innovator firms from the erosion of market share, mitigated by the decrease in support costs, the cost of completing a more detailed patent declaration, and the costs associated with the requirement that test data exist demonstrating ''sameness'' in order to submit a polymorph patent for listing. The estimated 1-year loss in revenues from

[2] The figure of $55.14 represents the hourly rate for ''lawyer'' from the Bureau of Labor Statistics 2003 National Compensation Survey of $38.77, and then adjusted for inflation at 1.58 percent (unadjusted CPI–U) and increased 40 percent to account for benefits.

[3] Pharmaceutical Industry Cost Savings Through Use of the Scale-up and Post-Approval Change Guidance for Immediate Release Solid Oral Dosage Forms (SUPAC–IR), prepared for FDA, 1998, p. 63.

erosion of market share is $3.160 billion and the reduction in support costs would reduce this loss by $142 million. We estimate the 1-year cost of providing the patent declaration information by completing the patent declaration forms is $293,000 and the cost associated with polymorph patents is $3.3 million. Thus, we estimate the 1-year cost to innovator firms is $3.022 billion.

We recognize that in projecting the future impact of this final rule, we must account for changes in the market for pharmaceuticals. The Office of the Actuary at CMS, projects that expenditures on prescription pharmaceuticals will increase dramatically in the near future. As in the proposed rule, we account for the projected growth in pharmaceutical expenditures by escalating our 1-year estimate by the annual CMS projected growth in prescription drug expenditures. We estimate the 10-year costs for the final rule are $51.584 billion. We annualized over the 10-year period at a 7 percent discount rate yields to obtain a cost of $4.871 billion.

D. Summary of Costs and Benefits

We estimate the 10-year cost of this final rule to be $51.584 billion and the annualized cost to be $4.871 billion. The 10-year benefit of this final rule is estimated to be $53.940 billion and the annualized benefit is $5.093 billion. These benefit and cost figures include the estimated impacts of an economic transfer. Thus, the 10-year net benefit is $2.356 billion and the annualized net benefit is $222 million. The quantified benefits exceed the quantified costs.

Moreover, there are benefits that are difficult to quantify. These benefits include reduced costs of litigation and more predictability in the business environment. The benefits to consumers also involve favorable secondary benefits, such as improved access to less expensive drugs. It also preserves the balance struck in the Hatch-Waxman Amendments.

E. Regulatory Alternatives

In creating this final rule, we considered several regulatory alternatives, including not enacting this rule. We rejected the alternative of not enacting this final rule because under the current situation, NDA holders and patent owners are able to use multiple 30-month stays to delay generic entry and frustrate the intent of the Hatch-Waxman Amendments. We considered allowing the submission of polymorph patents for listing in the Orange Book without the required test data demonstrating ''sameness.'' We rejected this alternative as we decided that a patent claiming different polymorphs of the active ingredient described in the NDA needed to have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. This requirement is similar to the requirement of establishing bioequivalence.

We also considered using the current system of patent declarations. This alternative was also rejected because the pre-existing declaration information may be insufficient to prevent NDA applicants and holders and patent owners from submitting patents to us that should not be submitted and listed under the act. The choices to require tests demonstrating ''sameness'' for polymorph patents and the required patent information provided in the patent declarations are particularly important in light of the fact that we lack the authority, expertise and resources to evaluate patents submitted to determine whether they should be listed in the Orange Book.

F. Small Business Impact

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. In the proposed rule, we certified that we believed the rule is not expected to have a significant impact on a substantial number of small entities, as we did not know of any small innovator companies that use or would use multiple 30-month stays to block entry from generic competitors. We did not receive comment on this certification and we continue to believe that this final rule will not have a significant impact on a substantial number of small entities.

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, 21 CFR part 314 is 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 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 a patent unless:

(i) The notice of the previous certification under § 314.50(i)(1)(i)(A)(*4*) was withdrawn or changed to a certification other than a certification under § 314.50(i)(1)(i)(A)(*4*); and

(ii) The 45-day period under section 505(c)(3) of the act had not expired; and

(iii) No person receiving notice under paragraphs (a)(1) and (a)(2) of this section had brought an action against the applicant for infringement of the patent that was the subject of the withdrawn or changed certification under § 314.50(i)(1)(i)(A)(*4*).

* * * * *

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

§ 314.53 Submission of patent information.

* * * * *

(b) *Patents for which information must be submitted and patents for which information must not be submitted*—(1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the required information on the declaration form set forth in paragraph (c) of this section for 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 (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. 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. For patents that claim a polymorph that is the same as the active ingredient described in the approved or pending application, the applicant shall certify in the declaration forms that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application. For patents that claim a drug product, the applicant shall submit information only on those patents that claim a drug product, as is defined in § 314.3, that is described in the 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 described in the pending or approved application. The applicant shall separately identify each pending or approved method of use and related patent claim. For approved applications, the applicant submitting the method-of-use patent shall identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) *Test Data for Submission of Patent Information for Patents That Claim a Polymorph*. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the new drug application product.

(c) *Reporting requirements*—(1) *General requirements*. An applicant described in paragraph (a) of this section shall submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is complete and submitted on the appropriate forms, FDA Forms 3542 or 3542a. These forms may be obtained on the Internet at http://www.fda.gov by searching for ''forms''.

(2) *Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents*—(i) *Original Declaration*. For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant shall submit FDA Form 3542a. The following information and verification is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) United States patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(I) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the new drug application;

(K) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent including the following:

(*1*) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the new drug application or supplement;

(*2*) Whether the patent claims a polymorph that is the same active ingredient that is described in the pending application or supplement;

(*3*) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(*4*) Whether the patent claims only a metabolite of the active ingredient; and

(*5*) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent including the following:

(*1*) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(*2*) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent including the following:

(*1*) Whether the patent claims one or more methods of using the drug product for which use approval is being sought and a description of each pending method of use or related indication and related patent claim of the patent being submitted; and

(*2*) Identification of the specific section of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted;

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval 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;

(Q) A signed verification which states: ''The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.''; and

(R) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(ii) *Submission of patent information upon and after approval.* Within 30 days after the date of approval of its application or supplement, the applicant shall submit FDA Form 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will rely only on the information submitted on this form and will not list or publish patent information if the patent declaration is incomplete or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the new drug application as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(4) of this section, patent information must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) Approval date of new drug application or supplement;

(H) United States patent number, issue date, and expiration date of patent submitted;

(I) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(J) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the new drug application;

(L) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent including the following:

(*1*) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the approved application;

(*2*) Whether the patent claims a polymorph that is the same as the active ingredient that is described in the approved application;

(*3*) Whether the applicant has test data, described at paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the approved application and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(*4*) Whether the patent claims only a metabolite of the active ingredient; and

(*5*) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent including the following:

(*1*) Whether the patent claims the approved drug product as defined in § 314.3; and

(*2*) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent including the following:

(*1*) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

(*2*) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and

(*3*) The description of the patented method of use as required for publication;

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition) or approved method(s) of use 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;

(R) A signed verification which states: ''The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.''; and

(S) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(3) *No relevant patents.* If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval, 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, the applicant will verify this information in the appropriate forms, FDA Forms 3542 or 3542a.

* * * * *

■ 4. Section 314.95 is amended by redesignating paragraph (a)(3) as paragraph (a)(4) and by adding new 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 if the applicant amends its application to add a certification under § 314.94(a)(12)(i)(A)(*4*) when the application already contained a certification under § 314.94(a)(12)(i)(A)(*4*) to a patent unless:

(i) The notice of the previous certification under § 314.94(a)(12)(i)(A)(*4*) was withdrawn or changed to a certification other than a certification under § 314.94(a)(12)(i)(A)(*4*);

(ii) The 45-day period under section 505(j)(5)(B)(iii) of the act had not expired; and

(iii) No person receiving notice under paragraphs (a)(1) and (a)(2) of this section had brought an action against the applicant for infringement of the patent that was the subject of the withdrawn or changed certification under § 314.94(a)(12)(i)(A)(*4*).

* * * * *

Dated: May 23, 2003.

Mark B. McClellan,

Commissioner of Food and Drugs.

Dated: June 9, 2003.

Tommy G. Thompson,

Secretary of Health and Human Services.

[This appendix will not appear in the Code of Federal Regulations.]

BILLING CODE 4160–01–S

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-XXXX
Expiration Date: XX-XX-XX
See OMB Statement on Page 3.

NDA NUMBER

NAME OF APPLICANT / NDA HOLDER

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

STRENGTH(S)

DOSAGE FORM

DRAFT

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval 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.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name	
Address	City/State
ZIP Code	Telephone Number
FAX Number *(if available)*	E-Mail Address *(if available)*

DRAFT

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-XXXX
Expiration Date: XX-XX-XX
See OMB Statement on Page 3.

NDA NUMBER

NAME OF APPLICANT / NDA HOLDER

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME

ACTIVE INGREDIENT(S)	STRENGTH(S)
DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT

DRAFT

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner		
	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞		
	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

DRAFT

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	☐ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in **4.2** claim an approved method of use of the approved drug product?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use 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. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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Food and Drug Administration
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5600 Fishers Lane
Rockville, MD 20857

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[FR Doc. 03–15065 Filed 6–12–03; 1:00 pm]
BILLING CODE 4160–01–S