Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Revisions to Implement Portions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 and Other Changes

PROPOSED RULE

RIN: 0910-AF97

SUPPORTING STATEMENT

A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The proposed rule would implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), which amended provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) that govern the approval of 505(b)(2) applications and abbreviated new drug applications (ANDAs). The proposed rule would implement portions of Title XI of the MMA that pertain to provision of notice to each patent owner and the new drug application (NDA) holder of certain patent certifications made by applicants submitting 505(b)(2) applications or ANDAs; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This proposed rule also would amend certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

The MMA was enacted on December 8, 2003, and superseded certain sections of the June 2003 final rule regarding the application of 30-month stays of approval of certain 505(b)(2) applications and ANDAs; the superseded regulations were subsequently

revoked by technical amendment (see "Application of 30-Month Stays on Approval of [ANDAs] and Certain [NDAs] Containing a Certification That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed; Technical Amendment" (69 FR 11309, March 10, 2004).

Title XI of the MMA addressed two key concerns identified in the FTC Report by limiting the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved (30-month stays) and by establishing conditions under which a first applicant would forfeit the 180-day exclusivity period such that approval of subsequent ANDAs would no longer be blocked. Section 1101 of the MMA provides that a 30-month stay of approval of a 505(b)(2) application or ANDA is available only if patent infringement litigation was initiated within the 45-day period after receipt of notice of a paragraph IV certification for a patent that had been submitted to FDA before the date of submission of the 505(b)(2) application or ANDA (excluding an amendment or supplement to the application). The resulting incentive for an applicant to change the listed drug relied upon through an amendment of or a supplement to a 505(b)(2) application or ANDA is addressed by the MMA's prohibition of the submission of certain types of changes (including those requiring reference to a different listed drug) in an amendment of or supplement to a 505(b)(2) application or ANDA. In addition, section 1101 of the MMA amended the FD&C Act to specify the types of court actions that will terminate a 30-month stay of approval.

Section 1101 of the MMA also created new requirements for 505(b)(2) and ANDA applicants sending notice of a paragraph IV certification, including changes to the timing and contents of such notice. In addition, the MMA established conditions under

which a 505(b)(2) or ANDA applicant may bring a declaratory judgment action to obtain "patent certainty" (i.e., obtain a judicial determination of non-infringement, invalidity, or unenforceability) with respect to a listed patent for which it has given notice of a paragraph IV certification but has not been sued by the NDA holder or patent owner(s) within the statutory timeframe. If a patent infringement action is initiated against the 505(b)(2) or ANDA applicant, the MMA provides that the applicant may assert a counterclaim seeking an order requiring a correction or deletion of the patent information submitted to FDA for listing by the NDA holder or patent owner.

Section 1102 of the MMA altered the conditions under which a 180-day period of marketing exclusivity is granted by requiring, among other things, that a first applicant lawfully maintain the paragraph IV certification contained in its submission of a substantially complete ANDA. In addition, section 1102 of the MMA established conditions under which a first applicant would forfeit the 180-day exclusivity period.

Section 1103 of the MMA clarified the types of bioavailability and bioequivalence data that can be used to support a 505(b)(2) application or ANDA for a drug that is not intended to be absorbed into the bloodstream.

We are currently implementing the 180-day exclusivity provisions of the MMA directly from the statute and will determine if additional rulemaking is necessary in the future. Where a novel issue of interpretation is raised by a particular factual scenario regarding forfeiture of 180-day exclusivity, we may open a public docket or otherwise seek comment from affected parties in advance of taking action.

2. Purpose and Use of the Information Collection

The proposed rule would implement portions of the MMA in a manner that preserves

the balance struck in the 1984 Hatch-Waxman Amendments between encouraging the availability of less expensive generic drugs and encouraging those who bring innovative new drugs to market. The proposed rule would also revise and clarify procedures related to the approval of 505(b)(2) applications and ANDAs, to reduce uncertainty among drug firms, reduce costs to industry, and reduce demands on FDA resources responding to industry inquiries.

The approval pathways for 505(b)(2) applications and ANDAs established by the Hatch-Waxman Amendments consider the competing interests of the entity that has developed information used to support approval of an NDA (including a 505(b)(2) application) and those wishing to rely on FDA's finding of safety and effectiveness for a drug approved in the NDA to support approval of their ANDA or 505(b)(2) application. Balance is achieved when competitors operate within the rules as intended. The market failure is that of a public good. Perfectly competitive markets are efficient, but in a static sense. Innovative behavior often leads to information that would be widely beneficial. When information is freely distributed and is both non-rivalrous and non-excludable, the innovator is unable to profit from its investment. Innovative behavior that would otherwise be socially beneficial will not take place, and the statically efficient market is dynamically inefficient. Our system of patents grants inventors a temporary right to their discoveries to allow them to benefit from their innovation. The Hatch-Waxman Amendments adjusted our system of rewarding innovation through patents and other forms of market exclusivity to strike a balance between static and dynamic efficiency in the market for pharmaceuticals.

Preserving the balance struck in the Hatch-Waxman Amendments requires public

intervention as a private entity will not voluntarily surrender a profitable advantage. Balance can be achieved through legislation, as was done in the MMA. Balance can also be addressed through regulation, as we propose. FDA has been implementing the MMA directly from the statute for several years and based on this experience has identified opportunities to clarify MMA provisions through the adoption of codified language. To the extent that clarified regulatory language improves certainty among regulated entities, this proposal, if promulgated, would reduce industry compliance costs and agency enforcement costs. FDA believes promulgation of regulation to be the appropriate mechanism to make known its practices in implementing the MMA and to obtain comment on the sometimes complicated rules FDA proposes to adopt as regulation.

The proposed rule would affect those submitting NDAs (including 505(b)(2) applications) and ANDAs for approval. Provisions of this rule would affect the submission of patent information by NDA holders for listing in the Orange Book and the submission by 505(b)(2) and ANDA applicants of a patent certification or statement addressing the listed patent(s) for the listed drug(s) relied upon or Reference Listed Drug (RLD), respectively. The proposed rule would also affect, for those certifying that a listed patent is invalid, unenforceable, or not infringed (paragraph IV certification), the requirements for the provision of notice of the paragraph IV certification to each patent owner and the NDA holder for the listed drug. The proposed rule would also affect other requirements associated with 505(b)(2) applications and ANDAs.

3. Use of Improved Information Technology and Burden Reduction

FDA has issued several guidance documents to explain the process for submitting and to encourage the submission of NDAs, ANDAs, and 505(b)(2) applications to the

Agency in electronic format. These guidance documents are available at FDA's guidance web site under "Electronic Submissions:"

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm

4. Efforts to Identify Duplication and Use of Similar Information

The information collection required as a result of these proposed revisions to 21 CFR 314 does not duplicate any other information collection.

5. Impact on Small Businesses or Other Small Entities

The following analysis is from the "IV. Analysis of Impacts" section of the proposed rule:

The proposed rule applies to applicants submitting NDAs (including 505(b)(2) applications) and ANDAs and to NDA and ANDA holders. According to the Table of Small Business Size Standards, the U.S. Small Business Administration (SBA) considers pharmaceutical preparation manufacturing entities (NAICS 325412) with 750 or fewer employees to be small. Statistics on the classification of firms by employment size from the U.S. Bureau of the Census show that in 2005, at least 85 percent of pharmaceutical manufacturing entities had fewer than 500 employees and would have been considered small by SBA.

We have provided monetized estimates for $194,314 in benefits and $91,371 in costs. These costs of this proposed rule are generally small unit costs incurred across many entities. Our estimated unit costs for all but one item are less than $190 per unit. In the table below, we express the unit cost of an amendment to a patent certification in terms of hundredths of a percent of average establishment shipments. Excluding one item (505(b)(2) applicants providing a patent certification to a pharmaceutically

equivalent drug product), there are costs of $83,146 attributable to about 1,200 units. Some affected entities would face multiple unit costs of some type in a year, but even this circumstance would not approach a significant impact on a substantial number of small entities. For a unit cost of $190 to amount to 1 percent of average shipments among establishment with fewer than 5 employees, the entity would have to incur that cost more than 40 times.

This proposal would require 505(b)(2) applicants to identify a pharmaceutically equivalent drug product as a listed drug relied upon and comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for the pharmaceutically equivalent listed drug relied upon). The estimated cost of this provision is $4,113 per instance. As shown in the table below, for firms with fewer than 5 employees, the unit cost of this provision would be less than 1 percent of average firm shipments, below a range that has been cited as a threshold for significant impacts. For firms with 25 to 49 employees, which is a more likely lower bound for firms submitting 505(b)(2) applications, the unit cost of this provision would be less than 0.05 percent of average shipments. We do not believe such a cost constitutes a significant impact.

We lack the data to provide reliable estimates of impacts for our proposals to align submitted patent information with patent-protected intellectual property and implement an administrative consequence for failing to provide notice within the MMA-specified 20-day timeframe. In principle, either provision could result in a large impact, but we believe the likelihood to be very small. We find that this proposed rule will not have a significant impact on a substantial number of small entities, but the impact is

uncertain.

Small Entity Characteristics and the Impact of Unit Costs Attributable to this Proposed Rule

	Pharmaceutical Preparation Manufacturing (NAICS 325412)	
No. of Employees	<5	20-49
Total Value of Shipments ($1,000)	187,933	978,494
No. of Establishments	228	109
Average Value of Shipments ($)	824,268	8,977,009
Unit Costs of Identifying a Pharmaceutically Equivalent Drug Product as a Listed Drug Relied Upon per § 314.50(i)(1)(i)(C) as a Percentage of the Average Value of Shipments	0.50%	0.046%

6. Consequences of Collecting the Information Less Frequently

Part 314 establishes a reporting frequency that is dictated by the need to focus on potential problems concerning the safety and effectiveness of human drugs. Less frequent data collection would hinder early detection of such threats to the public health.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

Sections of 21 CFR 314 require reporting in less than 30 days. These are postmarketing reports and expedited notification to FDA and are necessary for the Agency to determine as soon as possible whether a threat to the public health exists that warrants immediate regulatory action.

More than an original and 2 copies of a submission is required (e.g., four copies of draft labeling or 12 copies of final printed labeling) in order to permit concurrent (and, consequently, quicker) review of the application.

Although applicants are required to submit proprietary, trade secret, and other confidential information, this information is protected under FDA regulations and the

FD&C Act (see Section 10).

The specific format and content requirements for application submissions is necessary to ensure complete submissions (and reduce the need for time-consuming resubmissions) and to assist FDA in efficient reviews.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

On March 3, 2004, FDA published a notice in the Federal Register entitled "Generic Drug Issues; Request for Comments" (69 FR 9982) which invited public comment to further identify issues related to the MMA provisions regarding 30-month stays, 180-day exclusivity, and bioavailability and bioequivalence, along with any suggestions for how to resolve those issues. Comments received in response to the Agency's Request for MMA Comments are addressed in the proposed, as appropriate.

This proposed rule includes a 90 day period for public comment. The comments will be summarized and responded to in the final rule.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under these requirements.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under section 310(j) of the FD&C Act.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden and Costs

12a. Estimates of Annualized Hour Burden

Respondents to this collection of information are NDA applicants (including 505(b)(2) applicants) and ANDA applicants, patent owners, and their representatives.

This proposed rule would implement portions of Title XI of the MMA that pertain to a 505(b)(2) or ANDA applicant's provision of notice of paragraph IV certification to each patent owner and the NDA holder; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This proposed rule also would amend certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

FDA currently has OMB approval for the collection of information entitled "Application for Food and Drug Administration Approval to Market a New Drug" (OMB Control Number 0910-0001). This collection of information includes, among other things:

• The requirements in §§ 314.50(i) and 314.94(a)(12) for submission of an appropriate patent certification or statement in a 505(b)(2) application or ANDA;

• The requirements in §§ 314.52 and 314.95 for a 505(b)(2) or ANDA applicant to send notice of any paragraph IV certification to each patent owner and the NDA holder and amend its 505(b)(2) application or ANDA to certify that notice has been provided and to document receipt of the notice;

• The content requirements in § 314.54 for a 505(b)(2) application;

• The requirements in §§ 314.60 and 314.96 for applicants that amend an unapproved 505(b)(2) application or ANDA, respectively;

• The requirements in §§ 314.70 and 314.97 for supplements submitted to FDA for certain changes to an approved 505(b)(2) application or ANDA;

• The requirements in §§ 314.90 and 314.99 for applicants that request waivers from FDA for compliance with §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively;

• The procedures in § 314.107(c) by which a first applicant notifies FDA of the date of first commercial marketing;

• The requirement in § 314.107(e) for an applicant to submit to FDA a copy of certain court decisions related to a patent that is the subject of a paragraph IV certification;

• The requirement in § 314.107(f) for a 505(b)(2) or ANDA applicant to notify FDA immediately of the filing of any legal action within 45 days of receipt of the notice of paragraph IV certification by each patent owner or the NDA holder; and

• The requirement in § 314.107(f) for a patent owner or NDA holder who is an exclusive patent licensee that waives its opportunity to file a legal action for patent infringement within the 45-day period to submit to FDA a waiver in the specified format.

FDA has OMB approval for the collection of information entitled “General Administrative Procedures: Citizen Petitions; Petition for Reconsideration or Stay of Action; Advisory Opinions” (OMB Control Number 0910-0183). This collection of information includes, among other things, the requirements in § 314.93 for submitting a

suitability petition in accordance with 21 CFR 10.20 and 10.30.

FDA also has received OMB approval for the collection of information entitled "Applications for Food and Drug Administration 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" (OMB Control Number 0910-0513). This collection of information includes the requirements in § 314.50(h) for submission of patent information in an NDA, an amendment, or a supplement, as described in § 314.53. Section 314.53 requires that an applicant submitting an NDA, an amendment, or a supplement, except as provided in § 314.53(d)(2), submit on Forms FDA 3542a and 3542 the required patent information described in this section.

We are not re-estimating these approved burdens in this document. Only the reporting burdens associated with the MMA's amendments to the FD&C Act and the proposed changes to parts 314 and 320 are estimated in this document.

Under section 505(b), (c), and (j) of the FD&C Act and this proposed rule, the following information would be submitted to FDA but is not currently approved by OMB under the PRA:

Proposed § 314.50(i)(1)(i)(C) would require a 505(b)(2) applicant to submit an appropriate patent certification or statement for each patent listed in the Orange Book for a drug product(s) that is pharmaceutically equivalent to the proposed drug product for which the 505(b)(2) application is submitted. Proposed § 314.54 would require a 505(b)(2) applicant to identify a pharmaceutically equivalent product as a listed drug relied upon and to comply with applicable regulatory requirements. Generally, 505(b)(2)

applications submitted for a proposed drug product for which there is an approved pharmaceutical equivalent already cite the pharmaceutically equivalent product as a listed drug relied upon to support approval. Therefore, we are not estimating a new burden for proposed § 314.54 at this time. Based on our experience reviewing 505(b)(2) applications, we estimate that proposed § 314.50(i)(1)(i)(C) may result in approximately two instances per year in which an applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon and comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for the pharmaceutically equivalent listed drug relied upon). Based on an estimated average of 2.6 patents by each NDA holder for listing in the Orange Book, we estimate that there will be 5.2 responses per year, and the burden hours associated with this requirement in proposed § 314.50(i)(1)(i)(C) will be approximately 2 hours per response. If the patent certification submitted pursuant to proposed § 314.50(i)(1)(i)(C) is a paragraph IV certification, the applicant also must comply with the requirements in § 314.52 for notice of paragraph IV certification, which add approximately 80 hours (15.33 hours per response) to the currently approved burden hours. This estimate reflects other proposals described in this section of the document that would reduce the currently approved burden for § 314.52 from 16 hours per response to 15 hours per response, and the additional content requirement in proposed § 314.52(c) that would increase the estimated burden by 0.33 hours per response. As previously noted, we are not re-estimating approved burdens in this document. Accordingly, the estimate provided for § 314.52(a), (b), (c), and (e) reflects the additional burden that may arise from the requirement in proposed § 314.50(i)

(1)(i)(C) if the 505(b)(2) applicant submits a paragraph IV certification. We separately describe and estimate the burden of the additional content requirement in proposed § 314.52(c) for the estimated average of seven 505(b)(2) applications filed per year that contain one or more paragraph IV certification.

Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii) would require a 505(b)(2) or ANDA applicant to amend its patent certification from a paragraph IV certification to a paragraph III certification after the court enters a final decision from which no appeal has been or can be taken, or signs a settlement order or consent decree with a finding of infringement (unless the patent also is found invalid). Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii) also would require a 505(b)(2) or ANDA applicant to submit an amended patent certification in certain circumstances after the NDA holder has requested to remove a patent or patent information from the list. Based on our experience and review of selected court decisions, we estimate that there are approximately 12 instances per year in which a party has submitted a court decision or order with a finding of infringement. In addition, there are approximately 24 instances per year in which the NDA holder has requested to remove a patent or patent information from the list and the patent or patent information has been removed. Based on our experience, we estimate that this requirement may result in approximately 36 and 108 instances per year in which an applicant amends its 505(b)(2) application or ANDA, respectively, to submit a revised patent certification, and the burden hours associated with this requirement will be approximately 2 hours per response. Proposed §§ 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(vi)(C)(1)(ii) would expressly codify the current requirement for a 505(b)(2) or ANDA applicant to submit a patent certification or statement if, after submission of the

application, a new patent is issued by the Patent and Trademark Office (PTO) that in the opinion of the applicant and to the best of its knowledge, claims the listed drug or an approved use for such listed drug and for which information is required to be filed by the NDA holder. The burden hours associated with compliance with current provisions of §§ 314.50(i)(1) through (i)(6) and 314.94(a)(12)(i) through (a)(12)(viii) are described in the burden hours estimate currently approved under OMB Control Number 0910-0001.

Proposed §§ 314.52(a) and 314.95(a) would expand the list of acceptable delivery methods that may be used to send notice of paragraph IV certification to the NDA holder and each patent owner, and thereby reduce the burden on applicants to submit, under current §§ 314.52(a) and (e), a request to FDA to use common alternate delivery methods. We receive approximately 205 written inquiries per year from 505(b)(2) or ANDA applicants requesting permission to send notice of paragraph IV certification by an overnight delivery service. Proposed §§ 314.52(a) and 314.95(a) would eliminate the requirement to submit a request to use a designated delivery service, as defined in proposed §§ 314.52(f) and 314.95(f). We estimate that approximately 95 percent of these written inquiries will no longer be required because the alternate delivery method would fall within the definition of a "designated delivery service" in proposed §§ 314.52(g) and 314.95(g).

Proposed §§ 314.52(c) and 314.95(c) would require that notice of paragraph IV certification contain a statement that the applicant has received the acknowledgment letter or the paragraph IV acknowledgment letter, as applicable. In addition, proposed § 314.52(c) would require that the notice of paragraph IV certification contain a statement that a 505(b)(2) application that contains any required bioavailability or

bioequivalence data has been submitted by the applicant and filed by FDA, as required by section 505(b)(3)(D)(i) of the FD&C Act. We estimate that these additional content requirements for the notice of paragraph IV certification would increase the burden of providing notice of paragraph IV certification by approximately 20 minutes. Based on an estimated average of 7 505(b)(2) applications filed per year that contain one or more paragraph IV certifications and 209 ANDAs received per year that contain one or more paragraph IV certifications, we estimate that there will be 21 and 627 responses per year, and the burden hours associated with this requirement will be approximately 20 minutes per response.

Proposed §§ 314.52(d)(1) and 314.95(d)(1) would require notice of paragraph IV certification regardless of whether notice has already been provided for another paragraph IV certification contained in the 505(b)(2) application or ANDA or an amendment or supplement to the 505(b)(2) application or ANDA, as required by section 505(b)(3)(B)(ii) and 505(j)(2)(B)(ii)(II) of the FD&C Act. Since enactment of the MMA, FDA has regulated directly from the statute and required notice of paragraph IV certification in these circumstances. Thus, the burden associated with this statutory requirement is reflected in the burden hours estimate for §§ 314.52 and 314.95 currently approved under OMB Control Number 0910-0001.

Proposed §§ 314.52(e) and 314.95(e) would permit a 505(b)(2) or ANDA applicant to submit a single amendment containing documentation of timely sending and receipt of notice of paragraph IV certification. Currently, an applicant is required to amend its 505(b)(2) application or ANDA both at the time of sending notice of paragraph IV certification and after the notice was received by each patent owner and the NDA

holder (see current §§ 314.52(b) and (e) and 314.95(b) and (e)). Proposed § 314.95(e) also would require an ANDA applicant to include in its amendment a dated printout of the Orange Book entry for the RLD. FDA has OMB approval for the burden hours estimate of 16 hours per response for the estimated 260 responses submitted annually to comply with §§ 314.52 and 314.95 (see OMB Control Number 0910-0001). We estimate that 2 hours of the 16 hours per response are attributable to compliance with current §§ 314.52(b) and (e) and 314.95(b) and (e). We estimate that the burden hours associated with the requirement in proposed §§ 314.52(e) and 314.95(e) (including submission of the dated printout of the Orange Book entry) would be approximately 1 hour per response for each of the estimated 7 and 209 responses per year by our updated estimate of 7 505(b)(2) applicants and 209 ANDA applicants whose applications were filed or received, as applicable, by FDA and contained one or more paragraph IV certifications. Therefore, the proposal would reduce the currently approved burden for §§ 314.52 and 314.95 by 1 hour.

Proposed § 314.53(c)(2) would decrease the patent information that NDA applicants are currently required to submit for listing in the Orange Book. Proposed § 314.53(c)(2) would require an NDA applicant to submit information on a previously submitted patent only if a patent is a reissued patent of a patent previously submitted for listing for the NDA or supplement. Proposed § 314.53(c)(2) would require submission of patent information on whether a drug substance patent claims a polymorph only if such patent claims only a polymorph that is the same active ingredient described in the NDA or supplement. Proposed § 314.53(c)(2) also would provide that an applicant that submits information for a patent that claims either the drug substance or drug product and

meets the requirements for patent listing on that basis is not required to provide information on whether that patent also claims the drug product or drug substance, respectively. The information collection resulting from current § 314.50(h) (citing § 314.53) and Form FDA 3542a has been approved by OMB under Control Number 0910-0153 for FDA's estimate of 20 hours per response. We estimate the proposed revisions to our regulations will reduce the time needed to complete Form FDA 3542a by approximately 3 hours per response.

Proposed § 314.53(d)(2) would enable FDA to reduce duplicative submission of patent information and require such information only for a supplement to change the dosage form or route of administration, to change the strength, to change the drug product from prescription to over-the-counter use, or to correct previously submitted patent information that differently or no longer claims the changed product.

Proposed § 314.53(f)(2) would expressly require correction or change of patent information if the NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, if the NDA holder is required by court order to amend patent information or withdraw a patent from the list, or if the term of a listed patent is extended under 35 U.S.C. 156(e). We estimate that these corrections and changes of patent information would result in approximately 62 submissions of Form FDA 3542 or other written submission, as provided in proposed § 314.53(f)(2)(iv), by approximately 39 NDA holders. We further estimate that the burden hours associated with the requirement in proposed § 314.53(f)(2) would be approximately 1 hour per response.

Section 505(b)(4)(A) and (j)(2)(D)(i) of the FD&C Act generally prohibit the

submission of certain types of changes in an amendment or a supplement to a 505(b)(2) application or an ANDA, respectively. Proposed §§ 314.60(e) and 314.70(h) would prohibit an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient, different route of administration, different dosage form, or certain differences in excipients that the drug proposed in the original submission of the 505(b)(2) application. These changes must be requested in a new 505(b)(2) application. This proposed requirement conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see Separate Marketing Application Guidance). Accordingly, the burden associated with this statutory requirement is reflected in the burden hours estimate for §§ 314.50 and 314.94 currently approved under OMB Control Number 0910-0001 for 505(b)(2) applications and ANDAs, respectively.

Proposed §§ 314.60(f), 314.70(i), 314.96(d), and 314.97(c) would require an applicant to submit a patent certification if approval is sought for either of the following types of amendments or supplements to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use; or (2) to add a new strength. Proposed §§ 314.60(f) and 314.96(d) also would require an applicant to submit a patent certification if approval is sought for either of the following types of amendments to a 505(b)(2) application or ANDA: (1) To make other than minor changes in product formulation; or (2) to change the physical form or crystalline structure of the active ingredient. Although currently the submission of a patent certification is required if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement,

as amended (thus the burden hours are currently approved under OMB Control Number 0910-0001), the patent certification requirements would be broadened under this proposed rule. We estimate that this requirement may result in approximately 6 and 4 instances per year in which an applicant is required to submit a patent certification with an amendment or supplement, respectively, to its 505(b)(2) application. We further estimate that this requirement may result in approximately 95 and 16 instances per year in which an applicant is required to submit a patent certification with an amendment or supplement, respectively, to its ANDA. The burden hours associated with these requirements are estimated to be approximately 2 hours per response.

Proposed §§ 314.96(c) and 314.97(b) would prohibit an ANDA applicant from amending or supplementing an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA. An applicant must submit a change of the RLD in a new ANDA. We estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting an amendment for a change of the RLD. We also estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting a supplement for a change of the RLD. We further estimate that the burden of submitting an ANDA and complying with applicable regulatory requirements, including any required study to demonstrate bioequivalence to the new RLD, will be approximately 288 hours for each of the estimated two responses per year.

Proposed § 314.107(e) would expand the scope of the court actions and documented agreements related to a patent described in § 314.107(b)(3) that are required to be submitted to FDA. Proposed § 314.107(e) also would require submission of any

court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified. FDA has OMB approval for the burden hours estimate of 30 minutes per response for the estimated 98 responses submitted annually by 25 505(b)(2) or ANDA applicants to comply with § 314.107(e) (see OMB Control Number 0910-0001). Based on our experience, we estimate that 140 505(b)(2) and ANDA applicants will be required to submit a copy of a court action, documented agreement, or written notification of appeal in approximately 310 instances per year. We continue to estimate that the burden associated with submitting a copy of these documents to FDA is approximately 30 minutes per response.

The estimated burden of the burden of this collection of information is described in the following table:

Table 1.--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
314.50(i)(1)	2	2.6	5.2	2	10.4
314.50(i)(6)	36	1	36	2	72
314.52(a), (b), (c), and (e)	2	2.6	5.2	15.33	79.7
314.52(c)	7	3	21	0.33 (20 minutes)	7
314.53(f)	39	1.5	62	1	62
314.60(f)	6	1	6	2	12
314.70(i)	4	1	4	2	8
314.94(a)(12)	108	1	108	2	216
314.95(c)	209	3	627	0.33 (20 minutes)	209
314.96(c)	1	1	1	288	288
314.96(d)	95	1	95	2	190
314.97(b)	1	1	1	288	288
314.97(c)	16	1	16	2	32
314.107(e)	140	2.2	310	0.5 (30 minutes)	155
					Total 1629.1

12b. Annualized Cost Burden Estimate

The following table from the “IV. Analysis of Impacts” section of the proposed rule provides a summary of the total costs of the proposed rule. These costs are explained in section IV of the proposed rule:

Section of Proposed rule	General Change	Annual Costs
IV.C.1. Definitions	Establish definitions.	
IV.C.2. Submission of Patent Information	Reduce innovator patent declaration requirements.	
	Require submission of corrected patent information (e.g., for patent term extensions) and describe procedures for withdrawal of patents that no longer meet the statutory requirements for listing.	$5,476 for 60 additional requests at $91.27 each.
	More clearly defines requirements for submission of information on method-of-use patents, facilitating generic "carve-out."	
IV.C.3. Patent Certification	Require 505(b)(2) applicants to provide a patent certification to a pharmaceutically equivalent drug product.	$8,225 for 2 instances requiring identification of a pharmaceutically equivalent product as a listed drug.
IV.C.4. Notice of Paragraph IV Certification	Expand the list of acceptable delivery methods for 505(b)(2) and ANDA applicants providing notice, reducing the need for formal requests to FDA.	
	Require 505(b)(2) and ANDA applicants to include a statement that it has received an acknowledgment letter or paragraph IV acknowledgment letter in its notice of paragraph IV certification. Requires 505(b)(2) applicants to include a statement on bioequivalence data, if appropriate.	$19,714 for additional information in 648 certifications.
	Allow for the submission of a single amendment for both documentation of timely sending and receipt of notice of the paragraph IV certification.	
	Establish administrative penalties for ANDA applicants failing to provide notice of paragraph IV certification within 20 days of receipt of an acknowledgment letter or paragraph IV acknowledgment letter from FDA.	
IV.C.5. Amended Patent Certifications	Require 505(b)(2) and ANDA applicants to amend patent certifications if no longer accurate.	$26,286 for 144 additional amendments to patent certifications.
IV.C.6. Patent Certification Requirements for Amendments and Supplements to	Require 505(b)(2) and ANDA applicants making certain changes to their products to submit a new patent certification.	$22,087 for additional certifications for 10 505(b)(2) applications and 111 ANDAs.

505(b)(2) Applications and ANDAs.		
IV.C.7. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and Amendments or Supplements to an ANDA That Reference a Different Listed Drug	Prohibit an applicant from amending or supplementing an ANDA to reference a different RLD. Instead, the applicant must submit a new ANDA.	Negligible, consistent with current practice under the statute.
IV.C.8. Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication For, or Other Change From, a Listed Drug	Establish requirements for 505(b)(2) applications to identify a pharmaceutically equivalent drug as a listed drug relied upon.	Expected impact small; generally in compliance.
IV.C.9. Petition to Request a Change From a Listed Drug	Clarify procedures for petitioned ANDAs.	Negligible, would codify current practice.
IV.C.10. Filing an NDA and Receiving an ANDA	Clarify FDA acknowledgment letter procedures.	Negligible, would codify current practice.
IV.C.11. Approval of an NDA and ANDA	Clarify definition of an approved application and procedures related to tentative approval.	Negligible, would codify current practice and address confusing language.
IV.C.12. Refusal to Approve an NDA or ANDA	Clarify that a waiver of an application requirement is a waiver of an approval requirement.	Negligible, would codify current practice.
IV.C.13. Date of Approval of a 505(b)(2) Application or ANDA	Revise the description of court actions relevant to the date of approval of a 505(b)(2) application or ANDA, and require submission of related documentation.	$9,583 for 210 additional notifications.
IV.C.14. Assessing Bioavailability and Bioequivalence for Drugs Not Intended to be Absorbed Into the Bloodstream	Codify statutory revisions in the regulations.	Negligible, would codify current practice.

IV.C.15. Miscellaneous Changes	Editorial changes.	Negligible.
Total Monetized Impacts		$91,371

13. Estimates of Other Total Annual Costs to Respondents and Recordkeepers/Capital Costs

All costs are listed under "12b. Estimates of Costs" above.

14. Annualized Cost to the Federal Government

Based on CDER's human resource allocation data, approximately 835 FTEs are devoted annually to reviewing the submissions under 21 CFR 314. If each FTE equals approximately $254,000 for these review activities, the total cost burden to the Federal Government would be $212,090,000. The Federal costs that would result from this proposed rule are covered in this cost estimate.

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

FDA does not intend to publish tabulated results of these information collection requirements.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

All forms associated with this collection bear the OMB approval date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.