Abbreviated New Drug Applications and 505(b)(2) Applications
OMB Control No. 0910-0786
RIN: 0910-AF97
SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

This information collection supports agency rulemaking. On October 6, 2016, the Food and Drug Administration (FDA, the agency, we) published a final rule entitled, "*Abbreviated New Drug Applications and 505(b)(2) Applications*," (the final rule) in the Federal Register (81 FR 69580) to implement new regulations at 21 CFR parts 314 and 320. The final rule implements portions of 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 final rule implements the 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. FDA has been implementing the MMA directly from the statute and based on this experience has identified opportunities to clarify MMA provisions through the adoption of codified language. The final rule also amends certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

Title XI of the MMA addressed two key concerns identified in a 2002 Federal Trade Commission (FTC) report on anticompetitive strategies that may delay access to generic drugs. Title XI of the MMA limits 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 establishes 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 certain 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.

Section 1102 of the MMA requires, among other things, that a first applicant lawfully maintain the paragraph IV certification contained in its submission of a substantially complete ANDA in order to maintain eligibility for 180-day exclusivity. 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 also 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 will determine if additional rulemaking related to 180-day exclusivity is necessary in the future.

2. Purpose and Use of the Information Collection

The final rule implements 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 bringing innovative new drugs to market. The final rule also revises and clarifies procedures related to the approval of 505(b)(2) applications and ANDAs to reduce uncertainty among drug firms, reduce costs to industry for some of these procedures, 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 an NDA to support approval of their ANDA or 505(b)(2) application. FDA has been implementing the MMA directly from the statute. To the extent that clarified regulatory language improves certainty among regulated entities, the final rule will reduce industry compliance costs and agency enforcement costs.

The final rule affects those submitting NDAs (including 505(b)(2) applications) and ANDAs for approval. Provisions of this rule affect the submission of patent information by NDA holders for listing in the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (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 final rule also affects, 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 final rule also affects other requirements associated with 505(b)(2) applications and ANDAs.

3. Use of Improved Information Technology and Burden Reduction

To assist respondents, FDA has issued several guidance documents to explain the process for submitting 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 (FDA has verified the Web site addresses, as of the date of this document, but Web sites are subject to change over time.). FDA will continue in its efforts to utilize and employ technology that will facilitate reporting for respondents to the information collection.

4. Efforts to Identify Duplication and Use of Similar Information

The agency is unaware of duplicative information collection. Because this new request will necessitate conforming revisions to Forms FDA 3542 and 3542a, currently approved under OMB Control No. 0910-0513, the agency will incorporate burden resulting from the form revisions into the associated collection as appropriate.

5. Impact on Small Businesses or Other Small Entities

The information collection applies to all applicants submitting NDAs (including 505(b)(2) applications) and ANDAs and to NDA and ANDA holders. FDA provides small business and industry assistance to respondents through the Center for Drug Evaluation and Research (CDER) and through the Division of Manufacturers Assistance and Training component in the Center for Biologics Evaluation and Research (CBER). These resources may be found on FDA's website at www.fda.gov.

6. Consequences of Collecting the Information Less Frequently

The information collection schedule is consistent with statutory requirements. Failure to collect the information within established timeframes could undermine the accuracy and completeness of patent information listed in the Orange Book and submission of an appropriate patent certification or statement under section 505(b)(2) and 505(j) of the FD&C Act. In turn, this may delay approval of 505(b)(2) applications and ANDAs that are otherwise eligible for approval.

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

Sections of 21 CFR 314 require reporting in less than 30 days to ensure, for example, that FDA has timely notice of the filing of legal actions against a 505(b)(2) or ANDA applicant and court actions that may affect the timing of approval of 505(b)(2) applications and ANDAs that are otherwise eligible for approval. To the extent that the regulations require reporting to occur

more frequently than the quarterly basis described in § 1320.5(d)(2)(i) in certain circumstances (e.g., submission of patent information within 30 days of issuance of a new patent), this is expressly required by section 505(c)(2) of the FD&C Act. 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).There are no other special circumstances for this collection of information.

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

On February 6, 2015, FDA published a proposed rule in the Federal Register entitled "*Abbreviated New Drug Applications and 505(b)(2) Applications*" (80 FR 6802) to implement portions of Title XI of the MMA and to revise and clarify FDA regulations relating to 505(b)(2) applications and ANDAs. FDA received 13 comment letters on the proposed rule, and FDA addresses these comments in the final rule. None of the comments received pertained to the information collection analysis. The comments may be found under docket no. FDA-2011-N-0830.

9. Explanation of Any Payment or Gift to Respondents

No payments or gifts are provided to respondents.

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 301(j) of the FD&C Act.

11. Justification for Sensitive Questions

The information collection does not contain questions of a sensitive nature.

12. Estimates of Annualized Hour Burden and Costs

12a. Estimates of Annualized Hour Burden

The final rule implements 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. The final rule also amends certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

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

Section 314.50(i)(1)(i)(C) requires a 505(b)(2) applicant to submit an appropriate patent certification or statement for each patent listed in the Orange Book for one drug product approved in an NDA that is pharmaceutically equivalent to the proposed drug product for which the original 505(b)(2) application is submitted and was approved before the original 505(b)(2) application was submitted. Section 314.54 also describes this requirement. In general, 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. However, based on our experience reviewing 505(b)(2) applications, we estimate that §§ 314.50(i)(1)(i)(C) may result in two instances per year in which an applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon and to comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for a pharmaceutically equivalent drug product approved in an NDA). Based on an average of 3.4 patents submitted by an NDA holder for listing in the Orange Book, we calculate that the two instances in which a 505(b)(2) applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon will result in 6.8 patent certifications or statements per year. The burden associated with this requirement in § 314.50(i)(1)(i)(C) is approximately 2 hours per response. In addition, if the patent certification submitted pursuant to § 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.

The burden estimate for sending notice of a paragraph IV certification reflects other changes that reduce the currently approved burden for § 314.52 from 16 hours per response to 15 hours per response, and the additional content requirement in § 314.52(c) that increases the estimated burden by 0.33 hours per response. We are providing an estimate of 15 respondents for § 314.52(a), (b), and (e) to reflect the additional burden that may arise from the requirement in § 314.50(i)(1)(i)(C) if the two 505(b)(2) applicants submit paragraph IV certifications and to update data regarding the estimated number of 505(b)(2) applications that contain one or more paragraph IV certifications, which adds approximately 675 hours (15 hours per response) to the currently approved burden. We separately describe and estimate the burden of the additional content requirement in § 314.52(c).

Sections 314.52(a) and 314.95(a) expand the 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 existing §§ 314.52(a) and (e), a request to FDA to use common alternate delivery methods. We receive approximately 390 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. Sections 314.52(a) and 314.95(a) eliminate the requirement to submit a request to use a designated delivery service, as defined in §§ 314.52(g) and 314.95(g). We estimate that approximately 97.5 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 §§ 314.52(g) and 314.95(g).

Sections 314.50(i)(6) and 314.94(a)(12)(viii) 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 and enters a settlement order or consent decree with a finding of infringement (unless the patent also is found invalid). Sections 314.50(i)(6) and 314.94(a)(12)(viii) also 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 receiving submissions of court decisions or orders with a finding of infringement, and instances in which the patent or patent information has been removed from the list at the request of the NDA holder, we estimate that this requirement may result in approximately 17 and 153 instances per year in which an applicant amends its 505(b)(2) application or ANDA, respectively, to submit a revised patent certification. The burden hours associated with this requirement will be approximately 2 hours per response.

Sections 314.50(i)(6)(iii)(A)(*2*) and 314.94(a)(12)(viii)(C)(*1*)(*ii*) 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 USPTO 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. There is no change to the burden currently approved under OMB control number 0910-0001.

Section 314.95(c) requires that the notice of paragraph IV certification contain a statement that the applicant has received the paragraph IV acknowledgment letter. In addition, § 314.52(c) requires 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 20 505(b)(2) applications filed per year that contain one or more paragraph IV certifications (plus the additional burden that may arise from the requirement in § 314.50(i)(1)(i)(C) if the 2 505(b)(2) applicants submit paragraph IV certifications) and 400 ANDAs received per year that contain one or more paragraph IV certifications, we estimate that there will be 60 and 1,200 responses per year, respectively, and the burden hours associated with this requirement will be approximately 20 minutes per response.

Sections 314.52(d)(1) and 314.95(d)(1) 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 (j)(2)(B)(ii)(II) of the FD&C Act. Since enactment of the MMA in 2003, FDA has regulated directly from the statute and required notice of paragraph IV certification in these circumstances, and the burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Sections 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 existing §§ 314.52(b) and (e) and 314.95(b) and (e)). Section 314.95(e) also requires an ANDA applicant to include in its amendment a dated printout of the Orange Book entry for the RLD. The burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Section 314.53(c)(2) decreases the patent information that NDA applicants are currently required to submit for listing in the Orange Book. Section 314.53(c)(2) requires 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. Section 314.53(c)(2) also provides 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. Section 314.53(c)(2) also modifies requirements for submission of patent information on method-of-use patents. FDA has revised the text of the forms on which patent information is submitted to FDA to conform to the regulatory changes made by the final rule (see revised Forms FDA 3542a and 3542, attached). FDA is requesting OMB approval of the revised Forms FDA 3542a and 3542 as part of our request for OMB approval of the information collection provisions in the final rule and as a change request to the collection of information approved by OMB under control number 0910-0513.

The information collection resulting from existing § 314.50(h) (citing § 314.53) and Form FDA 3542a has been approved by OMB under control number 0910-0513 for FDA's estimate of 20 hours per response. We previously estimated that the burden of Form FDA 3542a would fall by 3 hours per response. We now estimate that the burden for Form FDA 3542a will be reduced by 5 hours from 20 hours to 15 hours per response; we further estimate that the burden for Form FDA 3542 will increase by 5 hours from 5 to 10 hours per response. We have shifted a portion of the time spent preparing Form FDA 3542a to the estimated time preparing Form FDA 3542 to reflect the additional time spent by the NDA holder to develop the use code in accordance with FDA's revised regulations and identify the specific section(s) and subsection(s) of labeling that describe the specific approved method of use claimed by the patent. Because FDA receives more Forms FDA 3542a annually than Forms FDA 3542, the net effect is a modest reduction in the overall burden estimate associated with these Forms.

Section 314.53(d)(2) avoids duplicative submission of patent information that would accompany supplements to NDAs and requires such information only for a supplement to add or change the dosage form or route of administration, to add or change the strength, to change the drug product from prescription to OTC use, or to revise previously submitted patent information that differently or no longer claims the changed product.

Section 314.53(f)(1) provides a more detailed description of the procedure for patent listing disputes directed to the accuracy or relevance of submitted patent information, and establishes additional requirements for patent listing disputes directed to method-of-use claims. Based on

our experience, we estimate that there may be approximately 12 instances per year in which a person submits a patent listing dispute, and a corresponding 12 instances per year in which the NDA holder is required to respond to the patent listing dispute. In light of the additional requirements for patent listing disputes directed to method-of-use claims, we estimate that the burden associated with § 314.53(f)(1) will be approximately 10 hours per response.

Section 314.53(f)(2) expressly requires 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 39 submissions of Form FDA 3542 or other written submission, as provided in § 314.53(f)(2), by approximately 27 NDA holders. We further estimate that the burden hours associated with the requirement in § 314.53(f)(2) would be approximately 1 hour per response.

Sections 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. Sections 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 than 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 final 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 guidance for industry on "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" (December 2004)). Accordingly, the burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Sections 314.60(f) and 314.96(d) require an applicant to submit a patent certification if approval is sought for the following types of amendments to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in product formulation; or (4) 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, the patent certification requirements would be broadened under this regulation. We estimate that this broadened requirement may result in approximately six instances per year in which an applicant is required to submit a patent certification with an amendment to its 505(b)(2) application. We further estimate that this requirement may result in approximately 100 instances per year in which an applicant is required to submit a patent certification with an amendment to its ANDA. The burden hours associated with these requirements are estimated to be approximately 2 hours per response.

Sections 314.96(c) and 314.97(b) 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 300 hours for each of the estimated two responses per year.

Section 314.107(e) expands the scope of the court actions and written consent to approval related to a patent described in § 314.107(b)(3) that are required to be submitted to FDA. Section 314.107(e) also requires 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. Based on our experience, we estimate that 247 505(b)(2) and ANDA applicants will be required to submit a copy of a court action, written consent to approval, or written notification of appeal in approximately 494 instances per year. We continue to estimate that the burden associated with submitting a copy of these documents to FDA (as approved in OMB Control No. 0910-0001) is approximately 30 minutes per response.

Table 1 — Estimated Annual Reporting Burden[1]

21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (in hours)	Total hours
314.50(i)(1)	2	3.4	6.8	2	14
314.50(i)(6)	17	1	17	2	34
314.52(a), (b), and (e)	15	3	45	15	675
314.52(c)	22	3	66	0.33 (20 minutes)	22
314.53(f)(1)	24	1	24	10	240
314.53(f)(2)	27	1.4	39	1	39
314.60(f)	6	1	6	2	12
314.94(a)(12)(viii)	153	1	153	2	306
314.95(c)	400	3	1,200	0.33 (20 minutes)	400
314.96(c)	1	1	1	300	300
314.96(d)	100	1	100	2	200
314.97(b)	1	1	1	300	300
314.107(e)	247	2	494	0.5 (30 minutes)	247
TOTAL					**2,789**

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

12b. Annualized Cost Burden Estimate

Estimated costs of the rulemaking are discussed more fully in the agency's Final Regulatory Impact Analysis (FRIA) at section D, which may be found under docket no. FDA-2011-N-0830. With regard to the information collection elements specifically, FDA estimates an average pharmaceutical industry wage rate of $82.47 per hour for preparing and submitting the information collection requirements under 21 CFR 314. Accordingly, by multiplying the total number of burden hours by the labor cost to respondents, the agency estimates an annualized cost burden of $230,009 (2,789 burden hours x $82.47).

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

There are no capital or start-up costs associated with the information collection.

14. Annualized Cost to the Federal Government

Review of information submitted to the agency under the collection will be covered by existing resource allocations.

15. Explanation for Program Changes or Adjustments

This is a new information collection request.

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

Display of OMB Expiration Date is appropriate.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.