DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Abbreviated New Drug Applications and 505(b)(2) Applications

Docket No. FDA-2011-N-0830

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. INTRODUCTION AND SUMMARY

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because average costs per entity are small, and the regulatory requirement with the highest cost per instance would affect few if any of the smallest entities, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

Many provisions of this final rule codify current practice, but some elements will lead to changes that generate additional benefits and costs. Table 1 summarizes the benefits and costs of this final rule. The estimated annualized monetized benefits of this final rule are $215,247 at a 3 percent or 7 percent discount rate, while the estimated annualized monetized costs are $266,947 at a 3 percent discount rate and $275,925 at a 7 percent discount rate. We have also identified, but are unable to quantify, additional impacts from changes to submitted patent information.

Table 1--Summary of Benefits and Costs

	Benefits	Costs
One-time (Year 1) Cost for Reading the Rule	Not Applicable	$466,450
Annually Recurring Compliance Costs or Savings (Years 1-10)	$215,247	$213,858
Present Value at 3 Percent	$1,836,098	$2,277,116
Present Value at 7 Percent	$1,511,803	$1,937,983
Annualized Value at 3 Percent	$215,247	$266,947
Annualized Value at 7 Percent	$215,247	$275,925

The full analysis of economic impacts is available in the docket for this final rule (Ref. 2) and at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm .

A. Need for Regulation and the Objective of This Final Rule

This final rule implements portions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (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. This rule also revises and clarifies procedures related to the approval of 505(b)(2) applications and abbreviated new drug applications (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 a new drug application (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.

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; this type of market failure is known as a public good. 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 strike a balance between rewarding innovation through market exclusivity and improving access and affordability for generic drugs.

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. To the extent that clarified regulatory language improves certainty among regulated entities, this final rule will reduce industry compliance costs and agency enforcement costs. FDA believes promulgation of a regulation to be an appropriate mechanism to make known its practices in implementing the MMA.

This final rule will affect those submitting NDAs (including 505(b)(2) applications) and ANDAs for approval. Provisions of this rule will 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. This final rule will 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 final rule also affects other requirements associated with 505(b)(2) applications and ANDAs.

Over the years 2012 through 2014, FDA filed an average of 114 NDAs and 127 NDA supplements requiring a patent declaration each year (81 FR 5465, February 2, 2016). Over the same years, FDA approved an average of 96 NDAs and 104 NDA supplements requiring a patent declaration each year (81 FR 5465).

A 505(b)(2) application is an NDA for which one or more of the investigations described in section 505(b)(1)(A) of the FD&C Act and relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (section 505(b)(2) of the FD&C Act). FDA files approximately 62 new original 505(b)(2) applications per year. For a 505(b)(2) application that relies upon a listed drug, the application must contain an appropriate patent certification or statement for each patent listed for the listed drug(s) relied upon. Based on a review of past filings, we estimate that approximately 20 of the 62 505(b)(2) applications submitted each year will contain one or more paragraph IV certifications.

An ANDA generally is an application for a duplicate of a previously approved drug that is submitted under the abbreviated approval pathway described in section 505(j) of the FD&C Act. As described in § 314.94, an ANDA is required to contain a patent certification or statement for each patent listed in the Orange Book for its RLD. FDA receives approximately 1,181 original ANDAs each year. Based on a review of past filings, we estimate that approximately 400 of the original ANDAs submitted each year contain one or more paragraph IV certifications.

B. BACKGROUND

This final rule is part of a series of actions to balance the benefits from the availability of less expensive generic drugs and the need to reward those who bring innovative drugs to market, consistent with the Hatch-Waxman Amendments. In response to a 2002 report from the Federal Trade Commission, FDA published a proposed rule in 2002 and final rule in 2003 to address circumstances in which innovator drug firms obtained and listed additional patents after a drug was approved which resulted in a delay in generic competition due to multiple 30-month stays.[1] The MMA was enacted later in 2003, and Title XI of that statute included provisions that, among other things, limited the availability of 30-month stays of approval. Since the enactment of the MMA, FDA has been regulating directly from the statute. Although the MMA superseded certain provisions of the June 2003 final rule (which were subsequently revoked by technical amendment), remaining differences between current regulations and the requirements of the MMA result in operating procedures that are not codified, leading to potential confusion among firms. FDA is amending the regulations for consistency with the MMA and to make other changes related to 505(b)(2) applications and ANDAs. These changes will improve transparency and facilitate compliance and enforcement and are consistent with the balance struck in the Hatch-Waxman Amendments.

We discuss benefits and costs of a government action relative to a baseline. For this analysis, we assume that but for this rulemaking, FDA would continue with current practices, regulating directly from the statute. Our baseline in this analysis is therefore continued operation under the FD&C Act, as amended by the MMA, without the promulgation of these regulations.

C. Comments Received and Changes Made to the Regulatory Impact Analysis

FDA received 13 comments from the public on the proposed rule, none of which commented directly on the economic analysis of impacts. (FDA responds to the comments received in the preamble to this final rule.) Nevertheless, we have revised this analysis of impacts throughout for three broad reasons: to reflect changes in the final rule, to incorporate updated data, and to conform more closely to current best practices in regulatory analysis.

D. Benefits and Costs of the Final Rule

Many provisions of this final rule would codify current practice, but some elements will lead to changes that generate additional benefits and costs. We organize benefits and costs below by thematic sections. We have also identified, but are unable to quantify, impacts from changes to submitted patent information.

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[1] Federal Trade Commission "Generic Drug Entry Prior to Patent Expiration: An FTC Study," July 2002, available at http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf.

1. COST TO READ AND UNDERSTAND THE RULE

This final rule will affect applicants submitting NDAs (including 505(b)(2) applications) and ANDAs for approval as well as NDA and ANDA holders. Based on Orange Book data from January 2016, we estimate that there are currently 707 unique application holders; we use this number of current NDA and ANDA holders to proxy for the number of entities affected by the rule.

Individuals from affected entities will need to devote time to reading and understanding this final rule. Because this final rule will affect applicants and application holders across the board, usually with small impacts on individual application holders, we assume an average of one regulatory affairs specialist at each firm reads the final rule. We further estimate that each reader will spend about 4 hours.[2] In valuing the time spent learning about the rule and complying with its various provisions, we use a cost of $164.94 per hour; this is an increase compared with the hourly cost used throughout our analysis of the proposed rule.[3] With these assumptions the total cost for reading the rule will be approximately $466,450, as shown in Table 2.

Table 2—Cost for Reading the Rule

Number of application holders	707
Time to read the final rule (hrs)	4
Value of time ($/hr)	164.94
Total Cost ($)	**466,450**

[2] Because not all parts of the final rule will apply to each applicant, we assume portions of the rule may be skimmed quickly while other parts may be read more closely. We account for this by estimating the cost based on the preamble only. At an adult average reading speed of 200-250 words per minute, we estimate that it will take approximately 4 hours to read the preamble to this final rule.

[3] We continue to base our estimate of the opportunity cost of one hour on the mean hourly wage of a lawyer in the pharmaceutical industry but update from 2009 to 2015 wages. The 2015 wage is $82.47, according to the Bureau of Labor Statistics' 2015 National Industry-Specific Occupational Employment and Wage Estimates (Ref. 1), compared with $70.64 in 2009. In addition, in the PRIA, we escalated the wage cost by 29.3 percent to account for employee benefits. In this FRIA, we have updated our methodology in accordance with current best practices and HHS guidance, and we double the wage to account for both employee benefits and overhead costs.

2. DEFINITIONS

This final rule would add several definitions to § 314.3(b), many of which are used in current practice. Some of the added definitions are not part of current practice but have been added in order to facilitate the enforcement of the FD&C Act, as amended by the MMA. We have not significantly changed any currently codified definitions in this section of our regulations except to remove obsolete references or otherwise clarify the definition. In summary, we expect these definitions to provide beneficial clarity and to improve efficiency, but we do not quantify impacts.

Some of the additions would codify longstanding definitions for terms used by the Agency in the implementation of section 505(b) and (j) of the FD&C Act, the statutory sections pertaining to the approval of "innovative" and "generic" drugs. Codifying longstanding definitions improves the clarity of current regulations and is consistent with current practice. Other additions are definitions that are established in the MMA. Codifying these definitions also improves clarity and efficiency while being consistent with FDA's current practice operating under the statute.

Some definitions added in this final rule are new and are not part of current practice, but we do not estimate impacts for them. For example, there currently is no formal letter stating that FDA has determined that a 505(b)(2) application containing a paragraph IV certification is regarded as filed. We are designating the filing communication that generally is sent to the 505(b)(2) applicant not later than 14 calendar days after the 60-day filing date (sometimes referred to as the "74-day letter") as the "paragraph IV acknowledgment letter" for a 505(b)(2) application that contains a paragraph IV certification. Formally describing the "paragraph IV acknowledgement letter" in codified language creates recognized milestones useful for defining processes in the implementation of the MMA. Establishing a new process in the implementation of the MMA might create a burden (which we address in the appropriate section of this analysis), but merely codifying a new definition does not create a burden.

We define the term "postmark" to give effect to the intent of the MMA; however, it should be noted that our definition is broader than the common usage of the term. The MMA requires a 505(b)(2) or ANDA applicant to give notice of its paragraph IV certification not later than 20 days after the date of the postmark on the notice from FDA informing the applicant that the application has been filed. Neither current section 505 of the FD&C Act nor part 314 of our current regulations defines "postmark." A postmark is often defined in terms of the official mark stamped by the United States Postal Service on an item of mail to cancel the stamp and to record the date and place of sending or receiving.[4] The MMA, however, uses the date of the

[4] See Concise Oxford English Dictionary, 1122 (11th Ed. 2008).

postmark to establish a reliable, verifiable record governing the timing of an important communication (i.e., date from which the 20-day period for sending notice of a paragraph IV certification runs). Based on our experience implementing the MMA, we have found that defining a postmark narrowly as an official mark from the United States Postal Service is problematic because some filing communications mailed by the Agency are typically sent in a franked envelope that may not bear a postmark made by the United States Postal Service and, when used, postmarks may not always be legible on mailings. Such a narrow definition would also fail to anticipate the increasing role of electronic communications. The final rule defines "postmark" more broadly to facilitate compliance and anticipate the continued growth in the role of electronic communications.

3. SUBMISSION OF PATENT INFORMATION

We proposed several changes that would affect the submission of patent information and the burden of Forms FDA 3542a and 3542. Applicants are currently required to submit information on whether the patent has been previously submitted to FDA. We proposed to limit this requirement to identify previously submitted patent information to a patent that is a reissued patent of a patent previously submitted for listing in the Orange Book for the NDA or supplement. However, as explained in the preamble to this final rule, we are not finalizing this proposal to limit this requirement. For any patent that claims a polymorph that is the same as the active ingredient described in the NDA, NDA applicants currently submit information on whether the patent claims a polymorph, including test data. We are finalizing our proposal to narrow the submission requirements such that information on a polymorph is only required in circumstances in which the patent claims only a polymorph. This narrowing will reduce the burden on NDA applicants. We are finalizing our proposal providing that an applicant submitting information for a patent that claims the drug substance or the drug product need not also submit information on whether the patent also claims the drug product or drug substance, and vice-versa. We are finalizing our proposal to clarify that an NDA applicant or holder may submit a single Form FDA 3542a or Form FDA 3542 for a patent claiming more than one method of use, provided that each method of use is listed separately along with the patent claim number(s) of the patent claim(s) that corresponds to each pending or approved method of use. We are finalizing, with clarifying revisions, our proposal to expressly require that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for 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. We also are finalizing, with clarifying revisions, our proposal to require that the NDA holder submitting information on the method-of-use patent identify with specificity the section(s) and subsection(s) of approved product labeling that describe the method(s) of use claimed by the patent submitted.

Based on the changes to the final rule and our assessment of current baseline practices for Forms FDA 3542a and 3542, we have updated our estimate of the effects of this rule on the burdens for submitting Forms FDA 3542a and 3542. 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; we further estimate that the burden for Form FDA 3542 will increase by 5 hours from 5 to 10 hours. We have shifted a portion of the time spent preparing Form FDA 3542a to the estimated time spent 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 an annual cost savings.

In a recent analysis of patent declaration requirements, FDA estimated there will be 200 annual instances in which an NDA holder is affected by patent declaration requirements, based on an average of 96 NDA approvals and 104 supplement approvals per year (81 FR 5465). In these instances, the NDA holders submit an average of 3.4 declarations (including declarations of no relevant patent information), for a total of 680 patent declarations on Form FDA 3542 annually. A regulatory affairs specialist will perform the tasks associated with the submission of patent information. The 5 hour increase in average burden per patent declaration submitted on Form FDA 3542 yields a cost increase of approximately $825 per patent or $560,796 annually.

In the same recent analysis of patent declaration requirements, FDA estimated there will be 241 annual instances in which an NDA applicant will be affected by patent declaration requirements, based on an average of 114 NDAs and 127 supplements requiring a declaration filed each year (81 FR 5465). Applying this same ratio of patent declarations per instance to 241 NDA submissions subject to patent listing requirements implies that 819 patent declarations are submitted on Form FDA 3542a annually. The 5 hour reduction in average burden per patent declaration submitted on Form FDA 3542a yields a cost savings of approximately $825 per patent or $675,429 annually.

The net effect of the reduction in burden on Form FDA 3542a and increase in burden on Form FDA 3542 is an annual cost savings of $114,633.

Section 314.53(d)(2) avoids duplicative submission of patent information that would accompany supplements to NDAs. Current regulations broadly require the submission of patent information with supplements seeking approval for a change in formulation, to add a new indication or other condition of use, to change the strength, or to make any other patented change regarding the drug substance, drug product, or any method of use. Section

314.53(d)(2) more clearly defines and limits situations where submission of patent information would be required for a supplement and clarifies when an NDA holder would need to resubmit patent information that was previously submitted. This provision is expected to reduce costs to those submitting NDA supplements, but we have not estimated the anticipated savings.

We are finalizing, with revisions, changes to §§ 314.50(i)(4) and 314.94(a)(12)(vi) stating conditions under which an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information. As revised, an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent ("use code") will be considered untimely filed unless it is submitted within 30 days of patent issuance; within 30 days of approval of a corresponding change to product labeling; or within 30 days of a decision by the PTO or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). The amendment based on a PTO or Federal court decision must contain a copy of the decision, and the accompanying Form FDA 3542 must identify the decision as a change related to the patent in section 1.h of the form. We do not estimate the cost of providing this documentation because we do not know how often this would occur. This proposed revision is consistent with the objective of ensuring that prospective 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug. Finally, method-of-use patent information that is untimely filed generally does not require a patent certification or statement by an applicant with a pending 505(b)(2) application or ANDA and thus would not delay approval of a pending 505(b)(2) application or ANDA.

Section 314.53(f)(2) establishes circumstances under which an NDA holder is required to correct listed patent information. If an NDA holder determines a patent no longer meets the statutory requirements for listing, or is required by court order to amend or withdraw the patent information, or if the term of the patent is extended under statutory provisions to compensate patent holders for regulatory review time, the NDA holder is required to correct or change the patent information. The request to correct patent information would be prepared by a regulatory affairs specialist who would prepare a new Form FDA 3542 and the process would take about 1 hour per request. We recognize that certain events (e.g., patent term extensions) for some NDAs would require changes for multiple patent listings. We have updated our estimates based on more recent experience. We now estimate that under section 314.53(f)(2) there will be 27 additional annual instances in which an NDA holder will be required to prepare a request to change patent information and that this will result in 39 additional changes to patent information. At an estimate of 1 hour per request, the estimated cost is $164.94 per request or $6,433 for all 39 requests.

Some patents claim a method of using a drug. Section 314.53(b)(1) more clearly aligns the requirements for submitting information on such method-of-use patents with the intent of the Hatch-Waxman Amendments. The Hatch-Waxman Amendments are based on a system in which accurate listed patent information assists 505(b)(2) and ANDA applicants (referred to as "generic applicants" or "generic application holders" for purposes of this analysis) in preparing their applications and determining whether their applications seek approval for a drug or method of using a drug that is claimed by a listed patent. Current regulations require NDA holders to identify the specific section of the proposed labeling that corresponds to the method of use claimed by the patent and to submit on Form FDA 3542 a description of the patented method of use ("use code") as required for publication in the Orange Book. NDA holders currently are instructed to provide a use code that contains "adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval" (Form FDA 3542). In reviewing generic applications, the Agency generally relies on the use code information provided by the NDA holder (and does not conduct an independent analysis of the scope of the patent) and uses this information to determine whether the proposed application is seeking approval for a method of use claimed by the listed patent.

This final rule requires identification of the specific section(s) and sub-section(s) of the proposed or approved labeling for the drug product that describes the method of use claimed by the patent submitted. The final rule also explicitly requires that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the use code must describe only the specific approved method of use claimed by the patent for 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. By limiting the patent use code to the approved method(s) of use claimed by the patent, a labeling carve-out based on the use code should appropriately protect the intellectual property rights of the NDA holder and patent owner. By revising the regulations to address an overbroad or ambiguous description of the approved method(s) of use claimed by a listed patent, the final rule is intended to remove a barrier to submission or approval of a 505(b)(2) application or an ANDA for uses that are not claimed by a listed patent.

We proposed to revise § 314.53(f)(1) to clarify and improve the mechanism for challenging the accuracy or relevance of patent information submitted to the Agency under § 314.53 and listed in the Orange Book. We proposed to establish a 30-day timeframe in which the NDA holder would be required to respond to FDA's request to confirm the correctness or omission of patent information to facilitate timely resolution of the patent listing dispute. We also proposed enhanced procedures to govern challenges to the accuracy or relevance of an NDA holder's submission of method-of-use patent information. We are finalizing the 30-day

timeframe for an NDA holder to respond to a patent listing dispute and are finalizing, with revisions, procedures to govern challenges to the accuracy or relevance of an NDA holder's submission of patent information. However, as described in the preamble to this final rule, at this time we are not finalizing our proposal to review a proposed labeling carve-out with deference to the applicant(s)' interpretation of the scope of the patent in certain circumstances. (We will continue to consider whether there is a need to finalize this proposal in the future.) Our changes to § 314.53(f)(1) to clarify and improve the mechanism for challenging the accuracy or relevance of patent information are expected to affect the burden of submitting and responding to these challenges. We currently receive approximately 12 patent listing disputes each year. We are unable to forecast whether or how much the number of disputes will change under this final rule. We estimate, based on recent patent listing disputes, that a person (including a 505(b)(2) or ANDA applicant) spends approximately 3 hours submitting a dispute and an NDA holder spends, on average, 2 hours responding to a patent listing dispute. We estimate that with our revisions to the process, it will take the person (including a 505(b)(2) or ANDA applicant) 10 hours to submit a dispute, an increase of 7 hours from the status quo. We also estimate that it will take the NDA holder 10 hours to respond to a dispute, an increase of 8 hours from the status quo. The total estimated increase in costs is then $13,855 for submitters of disputes, $15,834 for NDA holders, and $29,689 in total each year.

If an NDA holder submits patent information that includes a description of the patented method of use (i.e., the use code) that is broader than the actual scope of the patent claim(s), a generic applicant can: (1) carve out the labeling corresponding to the overbroad use code and seek approval for the remaining conditions of use, if any (assuming the drug product remains safe and effective for the remaining non-protected conditions of use with the labeling corresponding to the overbroad use code carved out); (2) submit a paragraph III certification and delay approval until patent expiry; or (3) submit a paragraph IV certification and proposed labeling that includes the patented method of use with the potential to be sued by the NDA holder or patent owner. For an overbroad use code that incorrectly suggests that the patent covers the entire indication or other essential condition(s) of use, as a practical matter a carve-out such as that described in scenario (1) may be precluded because there would be no way to label the drug safely for the remaining non-protected conditions of use without including, for example, the sole approved indication. It is this outcome, among others, that the final rule seeks to address where the patent itself is narrower than the use code provided and where, had the use code been described more precisely to correspond to the scope of the patent, a labeling carve-out would have been viable. If the generic applicant instead pursues scenario (3) and submits a paragraph IV certification for an overbroad use code and the NDA holder for the RLD or patent owner initiates patent infringement litigation, then the generic applicant can file a counterclaim seeking to correct the use code. If the counterclaim is successful, the NDA

holder would revise its use code and the generic applicant can amend its application to change its patent certification to a statement and carve out the narrower method of use that is actually claimed by the patent. This process can be time-consuming and can result in delayed marketing of a proposed drug product that is otherwise ready for approval.

To quantify the potential effects of revising the regulations to address an overbroad or ambiguous description of the approved method(s) of use claimed by a listed patent and clarifying and improving the mechanism for challenging the accuracy or relevance of patent information, we would need a baseline estimate of the likelihood of scenarios (2) and (3) and an estimate of the degree to which timing of generic entry would change as a result of these provisions. Monetization of effects from reducing delays in generic drug market entry, such as transfers in sales revenues from the NDA holder to the generic application holder along with consumer surplus gains from lower prices, would require data on market size and data on the elasticity of supply and demand of the affected markets. We do not know the likelihood that in the future an NDA holder would submit an overbroad use code that will not be consistent with the requirements under this final rule. We also do not know the extent to which making even more explicit the requirement that the use code be crafted narrowly to correspond to the specific approved method(s) of use claimed by the patent and improving the mechanism for challenging the accuracy or relevance of patent information will help generic applicants determine whether their applications do not seek approval for a use claimed by a listed patent, which would allow these applicants to submit a statement that the method-of-use patent does not claim a use for which the applicant is seeking approval (under scenario (1)) instead of a paragraph III certification or a paragraph IV certification (under scenarios (2) and (3)). For these reasons, we do not quantify the potential effects of these provisions.

4. PATENT CERTIFICATION

Section 314.50(i)(1)(i)(C) requires a 505(b)(2) applicant to submit a patent certification or statement for each patent listed in the Orange Book for one drug product that was approved in an NDA before the date of submission of the original 505(b)(2) application and is pharmaceutically equivalent to the proposed drug product in the original 505(b)(2) application. In our experience, a 505(b)(2) application generally will cite a pharmaceutically equivalent product as a listed drug, and we assume that without this rule, failure to do so would occur twice per year. Applying our estimate of 3.4 patents in the Orange Book per NDA holder, this provision will result in 6.8 additional submissions per year. Based on our experience, composing the submission will require 2 hours of work by a regulatory affairs specialist, for a total of 13.6 hours. If the patent certification is a paragraph IV certification, the applicant will face additional requirements for notice of paragraph IV certification, which require an

additional 15.33 hours of work.[5] Based on recent agency experience, we estimate that 505(b)(2) applications that contain at least 1 paragraph IV certification contain an average of 3 such certifications. Therefore, we estimate that 6 of the additional submissions per year are paragraph IV certifications, which results in an additional burden of approximately 92 hours. The estimated annual cost of this requirement is approximately 105.6 hours at $164.94 per hour or $17,414.

5. NOTICE OF PARAGRAPH IV CERTIFICATION

Sections 314.52(a) and 314.95(a) expand the acceptable methods for 505(b)(2) or ANDA applicants to provide notice of paragraph IV certification by permitting applicants to provide notice using designated delivery services, i.e., alternative delivery services that meet certain criteria. Expanding the methods by which a 505(b)(2) or ANDA applicant may send notice of paragraph IV certification reduces the need for such applicants to submit written requests to use an alternate delivery method. We currently receive about 390 such requests each year (an increase from approximately 200 per year we estimated for the proposed rule) and believe that 380 of the 390 will be unnecessary under the final rule. Assuming a request takes 30 minutes and is completed by a regulatory affairs specialist at $164.94 per hour, this change will reduce costs by $31,339 annually. Based on our experience with granting these requests, we can expand the acceptable delivery methods without creating costs elsewhere. This might also benefit applicants who are not currently submitting written requests but otherwise prefer to use an alternate delivery method.

This final rule changes the required contents of the notice of paragraph IV certification. Section 314.95(c) requires that an ANDA applicant's notice of paragraph IV certification contain a statement that the paragraph IV acknowledgment letter has been received to ensure that notice is not sent prematurely for an application that FDA ultimately decides to refuse to receive. As described in the preamble to this final rule, we are not finalizing our proposal under 314.52(c) requiring a 505(b)(2) applicant to include a statement that it has received a paragraph IV acknowledgment letter. However, existing regulations require a statement that the 505(b)(2) application has been filed (see § 314.52(c)(1)). Including this statement in the notice of certification will confirm that the required notice for a 505(b)(2) application is not sent prematurely. In addition, section 314.52(c) requires that the notice include a statement that a

[5] We have in the past (76 FR 20680 at 20683, April 13, 2011) estimated the information collection requirements associated with § 314.52 to require 16 hours of work. We assume other revisions to this section reduce this burden by 1 hour, but that section 314.52(c) will result in an additional 20 minutes of work. The total time burden estimated for section 314.50(i)(1)(i)(C) is 2 hours plus, if notice of paragraph IV certification is required, an additional 15.33 hours.

505(b)(2) application containing any required bioavailability or bioequivalence data has been submitted by the applicant and filed by FDA. As discussed above, we currently estimate that 20 505(b)(2) applications and 400 ANDAs are filed each year with paragraph IV certifications; these applications contain, on average, 3 paragraph IV certifications to listed patents. The 420 applications with paragraph IV certifications will result in 1,260 affected patent certifications. Based on experience with similar provisions, we estimate that a regulatory affairs specialist will spend an additional 20 minutes on each paragraph IV certification, for 420 additional hours at a total cost of $69,275. There will be additional costs associated with paragraph IV certifications for 505(b)(2) and ANDA supplements as well, but due to data limitations we are unable to quantify those costs.

Sections 314.52(d)(1) and 314.95(d)(1) codify the statutory requirement, added by the MMA, for 505(b)(2) and ANDA applicants to provide notice for all paragraph IV certifications, regardless of whether the applicant had previously given notice of a paragraph IV certification contained in its application or in an amendment or supplement to the application. These provisions codify current practice and will not result in additional costs.

Sections 314.52(b), 314.52(e), 314.95(b) and 314.95(e) allow a 505(b)(2) or ANDA applicant to submit a single amendment that includes: certification that notice has been provided to the NDA holder and each patent owner as required by §§ 314.52(a) and 314.95(a), respectively, and the notice met the content requirements described in §§ 314.52(c) and 314.95(c), respectively; documentation of timely sending of notice of the paragraph IV certification; and documentation of timely receipt of notice of the paragraph IV certification. (This is a modification of our proposal, under which an applicant still would need to amend its 505(b)(2) application or ANDA at the time that it provides notice of a paragraph IV certification with a statement certifying that notice has been provided and that the notice met the content requirements.) As applicants are currently required to submit at least two separate amendments, the consolidation into a single amendment will reduce costs. Section 314.95(e) also requires the ANDA applicant submit a dated printout of the entry for the RLD in the Orange Book, demonstrating that the paragraph IV certification was not sent prematurely. We estimate the 20 505(b)(2) applicants and 400 ANDA applicants with paragraph IV certifications will spend 1 hour less per certification, while the cost of submitting the page from the Orange Book will be negligible. At $164.94 per hour, the estimated cost reduction for 420 responses is $69,275.

The MMA explicitly requires that applicants making paragraph IV certifications provide notice within 20 days of the postmark on the FDA notification letter, but does not specify consequences for failing to meet this deadline (section 1101(a)(1)(A) of the MMA). For reasons described in the preamble to this final rule, we are not finalizing proposed § 314.101(b)(4),

which would have created an administrative consequence to encourage compliance with MMA by delaying the submission date of an ANDA by the number of days the applicant exceeded the statutory timeframe for providing notice. The impact of this proposal was not quantified in the proposed RIA.

6. AMENDED PATENT CERTIFICATIONS

Under certain circumstances, an applicant with a 505(b)(2) application or ANDA may need to amend a previously submitted patent certification. For example, a 505(b)(2) or ANDA applicant is required to amend its previously submitted patent certification if it is no longer accurate. In addition, a 505(b)(2) and ANDA applicant must submit a patent certification or statement to a newly issued patent for which patent information is timely filed by the NDA holder for the listed drug. Sections 314.50(i)(6) and 314.94(a)(12)(viii) require a 505(b)(2) or ANDA applicant to amend the patent certification from a paragraph IV certification to a paragraph III certification after a court enters a final decision or signs and enters a settlement order or consent decree with a finding of infringement. These provisions also require an applicant to amend a patent certification in certain circumstances when an NDA holder has requested to remove patent information from the list. We do not know with certainty the annual number of patents for which a patent certification will need to be revised, nor do we know for each such patent, the number of 505(b)(2) and ANDA applicants that will be required to amend their certification. Based on our experience, we estimate this requirement would result in 17 and 153 additional instances per year in which an applicant will amend its 505(b)(2) application or ANDA to submit a revised patent certification, respectively. At 2 hours per response and $164.94 per hour, the estimated cost of 170 responses is $56,080.

7. PATENT CERTIFICATION REQUIREMENTS FOR AMENDMENTS AND SUPPLEMENTS TO 505(b)(2) APPLICATIONS AND ANDAS

Certain amendments or supplements to a 505(b)(2) application or an ANDA have the potential to change an aspect of the proposed product in a way that changes the relationship between the proposed product and aspects of the listed drug relied upon or RLD, respectively, protected by a listed patent. Current regulations require an applicant to amend a certification if, at any time before approval of the 505(b)(2) application or ANDA, the applicant learns the certification is no longer accurate. We proposed revising the requirements to require that applicants submitting amendments or supplements for specified types of changes to their products would update their patent certifications and, if a paragraph IV certification, provide a new notice of paragraph IV certification that describes the basis for the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed. As discussed in the preamble to this final rule, after considering several comments on these proposals, we are finalizing the requirements for patent certifications for certain types of amendments to 505(b)(2)

applications and ANDAs but are not finalizing the proposed requirements for patent certifications for certain types of supplements at this time.

Section 314.60(f) requires an amendment to a 505(b)(2) application to contain a patent certification if it would make other than minor changes in product formulation, change the physical form or crystalline structure of the active ingredient, add a new indication or other condition of use, or add a new strength. The applicant will be required to provide a patent certification and, if a paragraph IV certification, provide notice of the paragraph IV certification that includes the basis for the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed. This may result in some new costs for 505(b)(2) applicants for certain types of amendments. We do not have a precise estimate for how often this will occur, but we estimate six amendments will need to include a new certification each year, with each requiring 2 hours of time from a regulatory affairs specialist. The 6 additional certifications will require 12 hours of time at $164.94 per hour for an estimated cost of $1,979.

Section 314.96(d) applies the same patent certification requirements for amendments to ANDAs. We do not have a precise estimate for the number of amendments to ANDAs that will need to contain a new patent certification under these provisions, but we estimate the provision will require additional patent certifications for at least 100 amendments, a slight increase from our estimate for the proposed rule. The 100 additional patent certifications will require 200 hours of time at $164.94 per hour or $32,988. Combining the estimated costs for 505(b)(2) applicants and ANDAs, the estimated cost of these provisions is $34,967.

8. 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

Sections 314.60(e) and 314.70(h) implement section 505(b)(4)(A) of the FD&C Act by prohibiting 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 or other specified differences from the drug proposed in the original application. This prohibition is consistent with current practice as FDA currently requires applicants seeking to modify the proposed drug product to have a different active ingredient or to make other specified changes to submit the different proposed drug in a new application.

Sections 314.96(c) and 314.97(b) implement section 505(j)(2)(D)(i) of the FD&C Act by prohibiting an applicant from amending or supplementing an ANDA to seek approval of a drug referring to a different listed drug than the RLD identified in the ANDA. As an example, this will apply if an ANDA applicant seeks approval for a change from a listed drug in a petitioned ANDA, and an NDA applicant obtains approval for a drug product with the changes that are the subject of the ANDA applicant's petition while the petitioned ANDA is pending. The ANDA applicant will not be permitted to amend the pending petitioned ANDA to cite the newly approved

pharmaceutical equivalent as its RLD. Such a change will be required to be made in a new ANDA that references the newly approved pharmaceutical equivalent as its RLD. If an applicant with a pending ANDA needs to identify a newly listed drug as its RLD, it is required to submit a new ANDA (because an amendment or supplement is not permitted). Based on our experience, such situations are very unusual, perhaps occurring two times per year. Because this provision is consistent with current practice, estimated costs are negligible.

9. Procedure for Submission of a 505(b)(2) Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug

It is possible for a 505(b)(2) application to be submitted for a proposed drug that is pharmaceutically equivalent to a listed drug (and not eligible for approval in an ANDA). We are revising § 314.54 to require a 505(b)(2) application to identify one pharmaceutically equivalent drug approved in an NDA as a listed drug relied upon, if one or more such drug products is approved before the original 505(b)(2) application is submitted. In our experience, 505(b)(2) applicants generally cite a pharmaceutically equivalent product as a listed drug, and we assume that without this rule, failure to do so would occur twice per year. We estimate the cost of submitting a patent certification or statement for each patent listed in the Orange Book for a drug product that was approved before the date of submission of the original 505(b)(2) application and is pharmaceutically equivalent to the proposed drug product in the original 505(b)(2) application (as required by section 314.50(i)(1)(i)(C)), above. Any other costs from this provision will be too small to reliably estimate.

10. Petition to Request a Change From a Listed Drug

A suitability petition is a request to use the ANDA pathway when there are specified differences between the proposed drug and an RLD. It has long been FDA's policy to require that when there is a pharmaceutically equivalent RLD, the ANDA should refer to that drug and not submit a suitability petition based upon another listed drug. Section 314.93 codifies current practice. There may be some small benefit associated with fewer suitability petitions that would ultimately not be granted, but any quantifiable monetized benefit will be so small as to make reliable estimation impossible.

11. Filing an NDA and Receiving an ANDA

This final rule codifies FDA's practice of sending an acknowledgment letter or a paragraph IV acknowledgment letter to notify an ANDA applicant that its application has been received. It also codifies FDA's proposal to use the filing communication that generally is sent to the 505(b)(2) applicant not later than 14 calendar days after the 60-day filing date as the "paragraph IV acknowledgment letter" that notifies an applicant of the filing of a 505(b)(2) application that contains a paragraph IV certification. The final rule also removes outdated language regarding antibiotics, clarifies certain refuse-to-file or refuse-to-receive provisions as

applying to both NDAs and ANDAs, and more precisely describes the factors that FDA considers in determining whether an ANDA is incomplete on its face and the actions that an ANDA applicant may take following a refuse-to-receive decision. Because Section 314.101 does not differ from current practice, its impact will be negligible.

12. Approval of an NDA and ANDA

The proposed rule clarified that an application is approved on the date of the issuance of an approval letter and that a drug that is "tentatively approved" is not an approved drug. We are finalizing the definition of "date of approval" with technical amendments to incorporate the Improving Regulatory Transparency for New Medical Therapies Act (IRTNMTA) (Public Law 114-89), which addresses concerns that delays in scheduling a newly approved drug product may reduce an applicable exclusivity period that commences on the "date of approval." The revisions to § 314.105 will result in no additional costs.

13. Refusal to Approve an NDA or ANDA

Revisions to §§ 314.90, 314.99, 314.125, and 314.127 establish that a waiver of a submission requirement for an NDA or ANDA also waives that requirement as a condition for approval. Because the final rule codifies FDA's current approach, there will be no additional costs.

14. Date of Approval of a 505(b)(2) Application or ANDA

We are finalizing, with revisions, changes to section 314.107(e) to expand the requirements associated with the notification to FDA of court actions and written consent to approval. To ensure timely notification to FDA, we are requiring a 505(b)(2) or ANDA applicant to submit all required information to the appropriate division in FDA's Office of New Drugs or Office of Generic Drugs within 14 calendar days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable. It is current practice for applicants to notify FDA within 10 working days of a final judgment. We are expanding the set of actions that trigger the requirement to notify FDA within an established timeframe, now 14 calendar days. However, we have determined that the principle effect of this requirement will be to change the timing of these submissions, not to increase the total number of submissions, because applicants eventually submit this information (if applicable) to FDA under the status quo on their own initiative or upon request by FDA in order for FDA to determine when the application is eligible for approval. Therefore, the incremental cost of these changes will be negligible.

15. Assessing Bioavailability and Bioequivalence for Drugs Not Intended to be Absorbed Into the Bloodstream

For some drugs that are not intended to be absorbed into the bloodstream, the establishment of bioavailability and bioequivalence may not be straightforward. The MMA

explicitly authorizes FDA to establish methods for assessing the bioavailability and bioequivalence of these drugs. Section 320.23 codifies FDA's existing practice of establishing such methods and costs are expected to be negligible.

16. MISCELLANEOUS CHANGES

This final rule makes several minor editorial changes to current regulations. These changes involve making clarifications and updating terminology but are not intended to change the meaning of the affected regulations. These changes would be generally beneficial, but benefits would be too small to reliably quantify.

17. SUMMARY OF COSTS

Table 3 summarizes the provisions of this final rule and their associated benefits (compliance cost savings) or costs. Table 4 summarizes the total costs of this final rule.

Table 3-- Summary of Provisions

Section of This Document	General Change	Annual Benefits	Annual Costs
I.D.2 Definitions	Establish definitions.		
I.D.3. Submission of Patent Information	Modifications to innovator patent declaration requirements.	A net savings of $114,633 from saving 5 hours on each Form FDA 3542a and spending 5 more hours on each Form FDA 3542. (The number of Forms FDA 3542a that FDA receives exceeds the number of Forms FDA 3542 that FDA receives.)	
	States conditions under which an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information.	This is consistent with the objective of ensuring that prospective 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug. Method-of-use patent information that is untimely filed generally does not require a patent certification or statement by an applicant with a pending 505(b)(2) application or ANDA and thus would not delay approval of a pending 505(b)(2) application or ANDA.	If the amendment is based on a PTO or Federal court decision, it must contain a copy of the decision and the accompanying Form FDA 3542 must identify the decision as a change related to the patent in section 1.h of the form. We do not estimate the cost of providing this documentation because we do not know how often this would occur.
	Require submission of		$6,433 for 39 additional

Section of This Document	General Change	Annual Benefits	Annual Costs
	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.		requests at $164.94 each.
	More clearly defines requirements for submission of information on method-of-use patents, facilitating generic "carve-out."	Aligns submitted patent information with innovator intellectual property protected by patent. Potentially facilitates generic entrance into the market under certain circumstances.	
	Clarify and improve the mechanism and procedures governing challenges to the accuracy or relevance of an NDA holder's submission of patent information, including establishment of a 30-day timeframe for an NDA holder to respond to a patent listing dispute.	Potentially facilitates generic entrance into the market under certain circumstances.	Total increase in costs of $29,689 for 12 disputes per year. (An increase of $13,855 for people, including 505(b)(2) or ANDA applicants, to submit disputes and $15,834 for NDA holders to respond).
I.D.4. Patent Certification	Require 505(b)(2) applicants to provide a patent certification to one pharmaceutically equivalent drug product approved in an NDA.		$17,414 for 2 instances requiring identification of a pharmaceutically equivalent product as a listed drug.
I.D.5. Notice of Paragraph IV Certification	Expand the acceptable delivery methods for 505(b)(2) and ANDA applicants providing notice, reducing the need for formal requests to FDA.	$31,339 savings from 380 fewer requests for permission to use an alternate delivery method.	
	Require ANDA applicants to include a statement that it has received a 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.		$69,275 for additional information in 1,260 certifications.
	Allow for the submission of a single amendment including: certification that notice has	$69,275 for 420 fewer required responses.	

Section of This Document	General Change	Annual Benefits	Annual Costs
	been provided to the NDA holder and each patent owner as required by §§ 314.52(a) and 314.95(a) and the notice met the content requirements described in §§ 314.52(c) and 314.95(c), documentation of timely sending of notice of the paragraph IV certification, and documentation of timely receipt of notice of the paragraph IV certification.		
I.D.6. Amended Patent Certifications	Require 505(b)(2) and ANDA applicants to amend patent certifications if no longer accurate.		$56,080 for 170 additional amendments to patent certifications.
I.D.7. Patent Certification Requirements for Amendments and Supplements to 505(b)(2) Applications and ANDAs.	Require 505(b)(2) and ANDA applicants making certain changes to their products to submit a new patent certification. (We are finalizing the requirements for amendments to 505(b)(2) applications and ANDAs but are not finalizing the requirements for supplements at this time.)		$34,967 for additional certifications for 6 amendments to 505(b)(2) applications and 100 amendments to ANDAs.
I.D.8. 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 a 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient or other specified differences from the drug proposed in the original application. Prohibit an applicant from amending or supplementing an ANDA to reference a different RLD. Instead, the applicant must submit a new NDA or ANDA.		Negligible, consistent with current practice under the statute.
I.D.9. Procedure for Submission of a 505(b)(2) Application Requiring Investigations for Approval of a New	Establish requirements for 505(b)(2) applications to identify one pharmaceutically equivalent drug product approved in an NDA as a listed drug relied upon.		Above we estimate the cost of patent certifications for 2 annual instances requiring identification of a pharmaceutically equivalent product as a listed drug. Any other costs from this

Section of This Document	General Change	Annual Benefits	Annual Costs
Indication for, or Other Change From, a Listed Drug			provision will be too small to reliably estimate.
I.D.10. Petition to Request a Change From a Listed Drug	Clarify procedures for petitioned ANDAs.		Negligible, would codify current practice.
I.D.11 Filing an NDA and Receiving an ANDA	Clarify FDA procedures for paragraph IV acknowledgment letters and acknowledgment letters		Negligible, would codify current practice.
I.D.12. 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.
I.D.13. 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.
I.D.14. 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 within 14 calendar days.		Negligible. The principle effect of this requirement will be to change the timing of submissions because applicants eventually submit this information (if applicable) to FDA under the status quo on their own initiative or upon request by FDA in order for FDA to determine when the application is eligible for approval.
I.D.15. 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.
I.D.16. Miscellaneous Changes	Editorial changes.	Would address confusing language.	Negligible.
Annual Compliance Cost Savings and Costs		$215,247	$213,858

Table 4--Summary of Benefits and Costs

	Benefits	Costs
One-time (Year 1) Cost for Reading the Rule	Not Applicable	$466,450
Annually Recurring Compliance Costs or Savings (Years 1-10)	$215,247	$213,858
Present Value at 3 Percent	$1,836,098	$2,277,116
Present Value at 7 Percent	$1,511,803	$1,937,983
Annualized Value at 3 Percent	$215,247	$266,947
Annualized Value at 7 Percent	$215,247	$275,925

E. SMALL ENTITY ANALYSIS

The following analysis, together with other relevant sections of this analysis and the final rule, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

This final rule changes patent listing, patent certification, and 30-month stay regulations. It also updates regulations pertaining to the type of bioavailability and bioequivalence data that can be used to support 505(b)(2) applications and ANDAs. Revisions to the Agency's regulations in parts 314 and 320 implement portions of Title XI of the MMA and facilitate compliance with and enforcement of the FD&C Act.

The final rule applies to applicants submitting NDAs (including 505(b)(2) applications) and ANDAs and to NDA and ANDA holders. According to the February 2016 Table of Small Business Size Standards, the U.S. Small Business Administration (SBA) considers pharmaceutical preparation manufacturing entities (NAICS 325412) with 1,250 or fewer employees to be small. Statistics on the classification of establishments by employment size from the U.S. Bureau of the Census show that in 2007 and 2012, approximately 98 percent of pharmaceutical manufacturing establishments had fewer than 1,000 employees. (See Table 5.) Using 1,000 employees as the size cutoff closest to the SBA threshold, and using establishments as a proxy for firms, we estimate that at least 98 percent of pharmaceutical manufacturing firms are considered small by SBA.

Table 5: Size distribution of Pharmaceutical Preparation Manufacturing Establishments in the Economic Census, 2012 and 2007

	Number of Establishments (2012 Census)	Proportion of Establishments (2012 Census)	Number of Establishments (2007 Census)	Proportion of Establishments (2007 Census)
Establishments with 0 to 4 employees	349	30.0%	284	28.7%
Establishments with 5 to 9 employees	138	11.8%	124	12.5%
Establishments with 10 to 19 employees	136	11.7%	77	7.8%
Establishments with 20 to 49 employees	193	16.6%	163	16.4%
Establishments with 50 to 99 employees	102	8.8%	86	8.7%
Establishments with 100 to 249 employees	105	9.0%	114	11.5%
Establishments with 250 to 499 employees	89	7.6%	68	6.9%
Establishments with 500 to 999 employees	35	3.0%	53	5.3%
Establishments with 1,000 to 2,499 employees	12	1.0%	15	1.5%
Establishments with 2,500 employees or more	6	0.5%	7	0.7%
Total	1,165		991	

We have estimated costs of $680,308 in year 1 (including both the one-time cost to read the rule and the first annual compliance cost) and $213,858 in annually recurring compliance costs in years 2 through 10. The costs of this final rule are generally small unit costs incurred across many entities. Our estimated unit costs for all but one of the recurring costs are less than $1,350 per unit.

This final rule would require 505(b)(2) applicants to identify one pharmaceutically equivalent drug product approved in an NDA 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 $8,707 per instance. In Table 6, we express this unit cost as a percentage of the average value of establishment shipments from the 2012 and 2007 Economic Censuses. (We include both years because the value-of-shipments data are suppressed for some size categories for confidentiality reasons; we display the two smallest size categories for which data are available in each Census year.) As shown in Table 6 of this document, for firms with less than 5 employees, the cost of this provision would

be 1.03 percent of average shipments, below a range that has been cited as a threshold for significant impacts.[6] For firms with 20 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 0.1 percent of average shipments. We do not believe such a cost constitutes a significant impact.

In Table 6 we also express the average total cost per establishment, in both year one and subsequent years, as a percent of average value of shipments. Average costs in year 1 are approximately 0.11 percent of the average value of shipments of the smallest firms (those with fewer than 5 employees); average costs in years 2 through 10 are approximately 0.04 percent of the average value of shipments of the same small establishments.

We lack the data to provide reliable estimates of impacts for provisions that seek to align submitted patent information with patent-protected intellectual property.

We find that this final rule will not have a significant impact on a substantial number of small entities.

Table 6.-- Impact on Small Businesses of Costs Attributable to this Final Rule

	5 - 9 Employees (2012 Census)	50 – 99 Employees (2012 Census)	Fewer than 5 Employees (2007 Census)	20 – 49 Employees (2007 Census)
Total Value of Shipments ($1,000)	413,685	3,537,620	239,929	1,998,457
No. of Establishments	138	102	284	163
Average Value of Shipments ($)	2,997,717	34,682,549	844,820	12,260,472
Unit Costs of Identifying One 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 ($8,707)	0.29%	0.03%	1.03%	0.07%
Average cost per establishment in year 1 ($962) as a percentage of the average value of shipments (includes both the one-time cost to read the rule and the first annual compliance cost)	0.03%	0.00%	0.11%	0.01%
Average annual cost per Establishment in years 2 - 10 ($302) as a percentage of the average value of shipments	0.01%	0.00%	0.04%	0.00%

[6] Guidance issued by the Department of Health and Human Services suggests that a 3 to 5 percent impact on total costs or revenues on small entities could constitute a significant regulatory impact (Ref. 4).

II. REFERENCES

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