

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

Preliminary Regulatory Impact Analysis  
Initial Regulatory Flexibility Analysis  
Unfunded Mandates Reform Act Analysis

Economics Staff  
Office of Planning  
Office of Policy and Planning  
Office of the Commissioner

## I. Introduction and Summary

### A. Need for Regulation and the Objective of This Proposed Rule

### B. Background

### C. Benefits and Costs of the Proposed Rule

#### I.C.1. Definitions

#### I.C.2. Submission of Patent Information

#### I.C.3. Patent Certification

#### I.C.4. Notice of Paragraph IV Certification

#### I.C.5. Amended Patent Certifications

#### I.C.6. Patent Certification Requirements for Amendments and Supplements to 505(b)(2) Applications and ANDAs

#### I.C.7. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and Amendments or Supplements to an ANDA That Reference a Different Listed Drug

#### I.C.8. Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug

#### I.C.9. Petition to Request a Change From a Listed Drug

#### I.C.10. Filing an NDA and Receiving an ANDA

#### I.C.11. Approval of an NDA and ANDA

#### I.C.12. Refusal to Approve an NDA or ANDA

#### I.C.13. Date of Approval of a 505(b)(2) Application or ANDA

#### I.C.14. Assessing Bioavailability and Bioequivalence for Drugs Not Intended to be Absorbed Into the Bloodstream

#### I.C.15. Miscellaneous Changes

## II. References

## III. Technical Appendix A

## I. Introduction and Summary

FDA has examined the impacts of the proposed 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 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We do not believe this proposed rule would result in a significant impact on a substantial number of small entities, but the impacts are uncertain.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “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 \$141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

### I.A. Need for Regulation and the Objective of This Proposed Rule

This proposed rule would implement 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 would also revise and clarify 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, and reduce demands on FDA resources responding to industry inquiries.

The approval pathways for 505(b)(2) applications and ANDAs established by the Hatch-Waxman Amendments consider the competing interests of the entity that has developed information used to support approval of an NDA (including a 505(b)(2) application) and those wishing to rely on FDA's finding of safety and effectiveness for a drug approved in the NDA to support approval of their ANDA or 505(b)(2) application. Balance is achieved when competitors operate within the rules as intended.

The market failure is that of a public good. Innovative behavior often leads to information that would be widely beneficial. When information is freely distributed and is both non-rivalrous and non-excludable, the innovator is unable to profit from its investment. Innovative behavior that would otherwise be socially beneficial will not take place, and the statically efficient market is dynamically inefficient. Our system of patents grants inventors a temporary right to their discoveries to allow them to benefit from their innovation. The Hatch-Waxman Amendments strike a balance between rewarding innovation through patents and other forms of market exclusivity and improving access and affordability for generic drugs.

FDA has been implementing the MMA directly from the statute for several years and based on this experience has identified opportunities to clarify MMA provisions through the adoption of codified language. To the extent that clarified regulatory language improves certainty among regulated entities, this proposal, if promulgated, would reduce industry

compliance costs and agency enforcement costs. FDA believes promulgation of regulation to be the appropriate mechanism to make known its practices in implementing the MMA and to obtain comment on the rules FDA proposes to adopt.

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

For the years 2007-2009, FDA filed an average of 117 NDAs and 116 NDA supplements. Therefore, we assume 233 (=117+116) instances each year where an NDA applicant would be affected by patent listing requirements (see 75 FR 39531, July 9, 2010, for a previous analysis using the same estimate). A 505(b)(2) application is one 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 35 505(b)(2) applications per year. These applications are required to contain a 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 7 of the 35 505(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 800 ANDAs each year. Based on a review of past filings, we estimate that approximately one-fourth of the ANDAs submitted each year (i.e., approximately 200) contain one or more paragraph IV certifications.

#### I.B. Background

This proposal is part of a series of actions to preserve the balance struck in the Hatch-Waxman Amendments between benefits from the availability of less expensive generic drugs and the need to reward those who bring innovative drugs to market. 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.<sup>1</sup> The MMA was enacted later in 2003, and Title XI of that statute included provisions that, among other things, addressed the 30-month stay provisions. 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

---

<sup>1</sup> 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>.

among firms. FDA is proposing to amend the regulations for consistency with the MMA and to make other changes related to 505(b)(2) applications and ANDAs. These changes would improve transparency, facilitate compliance and enforcement, and preserve 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 the practices adopted after the enactment of the MMA in 2003. 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.

#### I.C. Benefits and Costs of the Proposed Rule

Although many provisions of this proposed rule would codify current practice, elements of this proposal would lead to changes that generate additional benefits and costs. We present benefits and costs below using the thematic sections from earlier in this document. The estimated annual monetized benefits of this proposed rule are \$194,314, and estimated annual monetized costs are \$91,371. We have also identified, but are unable to quantify, impacts from proposed changes to submitted patent information and the implementation of an administrative consequence for failing to provide notice within the timeframe specified by the MMA.

##### I.C.1. Definitions

This proposed rule would add several definitions to § 314.3(b), many of which are used in current practice. Some proposed definitions are not part of current practice but are proposed in order to facilitate the enforcement of the FD&C Act, as amended by the MMA. In summary, we expect these proposed definitions to provide beneficial clarity and to improve efficiency, but we do not quantify impacts.

Some of the proposed 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 “new” and “generic” drugs. Codifying longstanding definitions would improve the clarity of current regulations and would be consistent with current practice. Other proposed additions are definitions that are established in the MMA. Codifying these definitions would also improve clarity and efficiency while being consistent with FDA’s current practice operating under the statute.

Some proposed definitions in this proposed 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 “paragraph IV acknowledgment letter” stating that FDA has determined that a 505(b)(2) application containing a paragraph IV certification is regarded as filed. Formally establishing these communications 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 would not create a burden.

We do not propose to significantly change any currently codified definitions in this section of our regulations except to remove obsolete references or otherwise clarify the definition. We propose to define the term “postmark” to give effect to the intent of the MMA; however, it should be noted that our proposed 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.<sup>2</sup> The MMA, however, uses the date of the 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 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 proposed rule would define “postmark” more broadly to facilitate compliance and anticipate the continued growth in the role of electronic communications. We do not know of any negative impacts associated with our proposed definition. We invite comment on potential impacts that would be associated with adoption of this definition.

#### I.C.2. Submission of Patent Information

Proposed § 314.53(c)(2) would narrow the circumstances under which NDA applicants would be required to submit patent information on a previously submitted patent. Applicants are currently required to submit information on whether the patent has been previously submitted. We propose to limit this requirement to a patent that is a re-issued patent of a patent previously submitted for listing in the Orange Book for the NDA or supplement. In addition, for patents that claim a polymorph that is the same as the active ingredient, NDA applicants currently submit information on whether a patent claims a polymorph. We propose to narrow the submission requirements to circumstances in which the patent claims only a polymorph. Both of

---

<sup>2</sup> See Concise Oxford English Dictionary, 1122 (11th Ed. 2008).

these proposed changes would reduce the burden associated with the completion of Forms FDA 3542a and 3542. This proposed rule would further reduce the burdens associated with the submission of patent information by 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.

In a prior analysis of patent declaration requirements, FDA estimated that, on average, an NDA holder submits patent information on 2.6 patents per listed drug (75 FR 39531, July 9, 2010). Applying this ratio to the 233 NDA submissions subject to patent listing requirements implies 606 patents submitted for listing annually. Based on our experience with the submission of patent information, we estimate the proposal would reduce the average reporting burden per patent from 20 hours to 17 hours. A regulatory affairs specialist could perform the tasks associated with the submission of patent information. At a total hourly compensation rate of \$91.27, narrowing the reporting requirements would reduce costs associated with this provision by \$274 per patent or \$165,929 for the 606 patents submitted for listing annually.<sup>3</sup>

Proposed § 314.53(d)(2) would more closely target critical elements 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.

Proposed § 314.53(d)(2) would more clearly define situations where submission of patent information would be required for a supplement. This provision would reduce costs to those

---

<sup>3</sup> We assume the hourly cost of a regulatory affairs specialist to be \$70.64, which is the mean hourly wage of a lawyer in the pharmaceutical industry, according to the Bureau of Labor Statistics' 2009 National Industry-Specific Occupational Employment and Wage Estimates (Ref. 1). We obtain a total hourly compensation rate of \$91.27 by escalating the cost by 29.3 percent for average benefits, according to the Bureau of Labor Statistics' 2010 report on Employer Costs for Employee Compensation (Ref. 2).

submitting supplements, but savings would be so small as to make accurate estimation impossible.

Proposed § 314.53(f)(2) would establish circumstances under which an NDA holder would be 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 would be 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 an hour. We recognize triggering events for some NDAs would require changes for multiple patent listings. Based on our experience, we estimate that under proposed § 314.53(f)(2) there would be 45 additional annual instances where an NDA holder would be required to prepare a request to change patent information and that this would result in 60 additional changes to patent information. At 1 hour per request, the estimated cost is \$91.27 per request or \$5,476 for all 60 requests.

Some patents claim a method of using a drug. Proposed § 314.53(b)(1) would more clearly align 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 must start with the use code information provided by the NDA holder (rather than doing an independent analysis of the scope of the patent) and use this information to determine whether the proposed application is seeking approval for a method of use claimed by the listed patent.

This proposed rule would explicitly require that if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder’s use code must describe only the specific portion(s) of the indication or other method of use claimed by the patent. By requiring close alignment of the patent use code with the actual scope of the patent claims, the Agency would be appropriately protecting the intellectual property rights of the NDA holder. By expressly prohibiting an overbroad description of the method(s) of use claimed by a listed patent and, in certain scenarios, proposing to review a proposed labeling carve-out for the 505(b)(2) application or ANDA with reference to the generic applicant’s (rather than the NDA holder’s) interpretation of the scope of the patent, the proposal is intended to facilitate removal of an unwarranted barrier to submission or approval of a 505(b)(2) application or an ANDA for uses that are not claimed by a listed patent.

Under the status quo, 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 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. For an overbroad use code that purports to cover 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 that the proposed 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 initiates patent infringement litigation, then the generic applicant can file a counterclaim seeking to correct the use code. If the counterclaim is successful, the generic applicant can amend its application to revise its patent certification 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.

Under the proposed rule, if, despite the enhanced instructions for the content of a use code, an NDA holder submits an overbroad use code and other criteria are met, a generic applicant would not be required to file a counterclaim in a paragraph IV lawsuit (as described in scenario (3)) in order to align its labeling carve-out more closely to the actual scope of the patent. Instead, an applicant could propose a narrower labeling carve-out than the use code would

suggest and FDA would review the proposed labeling carve-out and determine whether the drug remains safe and effective for the remaining non-protected conditions of use with reference to the generic applicant's interpretation of the approved conditions of use that are within the scope of the patent, not with reference to the use code that the NDA holder provided. By removing certain barriers to use of the existing statutory mechanism for carving out labeling claimed by a patent, this provision is intended to prevent instances where an overbroad use code effectively causes a delay in generic entry because the generic applicant is limited as a practical matter to: scenarios (2) and (3) -- submitting a paragraph III certification that would delay approval until patent expiry or submitting a paragraph IV certification, respectively. The latter option may result in the generic applicant getting sued for patent infringement and provide an opportunity for that applicant to file a counterclaim to correct the use code, which could result in market entry before patent expiry ("early market entry").

To quantify the potential effects of this provision, 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 this provision. 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. Aside from information obtained from reported court decisions, we do not know the likelihood that an NDA holder would submit an overbroad use code that would not be permitted under this proposal (see, e.g., Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670 (2012)). 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 scope of the patent would 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), respectively).

In the simple case of an RLD with only one listed patent that claimed only a method of use, this approach would be expected to result in earlier market entry of the proposed drug product because approval would not be delayed by litigation or until patent expiry. However, as discussed in detail in the Technical Appendix, even in this relatively straightforward case, the circumstances that would lead to this outcome are unlikely. We also note that many new drugs are covered by multiple patents, including patents claiming the drug substance and/or the drug product, as well as various types of exclusivity. The ability of the generic applicant to “carve out” an unprotected method would be insufficient for earlier market entry if there are other non-method-of-use patents protecting exclusivity of the drug. Such complicating factors, for example, would make reducing delays in generic drug entry through the “carve out” provision unlikely. Accordingly, we cannot determine the likelihood that the proposed provision would actually reduce delays in generic drug entry. It also should be noted that if the 505(b)(2) or ANDA applicant misinterpreted the scope of the patent and did not carve out all protected method-of-use information, the applicant would be subject to patent infringement litigation upon approval of the drug and may be enjoined from marketing. Thus, assuming that the NDA holder can challenge the 505(b)(2) or ANDA applicant’s carve-out through litigation, that litigation would still take place if from the perspective of the NDA holder, the expected gain from

litigating is greater than the cost. As we are unable to empirically test these predictions, we request comment and data on the expected impact.

### I.C.3. Patent Certification

Proposed § 314.50(i)(1)(i)(C) would require a 505(b)(2) applicant to submit 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 505(b)(2) application and is pharmaceutically equivalent to the proposed drug product in the 505(b)(2) application. In our experience, it would be unusual for a 505(b)(2) application to fail to cite a pharmaceutically equivalent product as a listed drug, and we assume that without this rule, it would occur twice per year. Applying our estimate of 2.6 patents in the Orange Book per NDA holder, this proposal would result in 5.2 additional submissions per year. Based on our experience, composing the submission would require 2 hours of work by a regulatory affairs specialist. If the patent certification is a paragraph IV certification, the applicant would face additional requirements for notice of paragraph IV certification, which would require an additional 15.33 hours of work.<sup>4</sup> We do not have a reliable estimate for the fraction of additional submissions that would be paragraph IV certifications and we assume for this analysis that the 5.2 additional submissions per year are paragraph IV certifications which would result in a burden of 90.1 hours. The estimated annual cost of this proposed requirement is 90.1 hours at \$91.27 per hour or \$8,225.

### I.C.4. Notice of Paragraph IV Certification

Proposed §§ 314.52(a) and 314.95(a) would expand the list of acceptable methods for 505(b)(2) or ANDA applicants to provide notice of paragraph IV certification by permitting

---

<sup>4</sup> 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 proposals in this section would reduce this burden by 1 hour, but that proposed § 314.52(c) would result in an additional 20 minutes of work. The total time burden estimated for proposed § 314.50(i)(1)(i)(C) would be 2 hours plus, if notice of paragraph IV certification is required, 15.33 hours for 17.33 total hours.



applicants to provide notice using designated delivery services. Expanding the list of methods by which a 505(b)(2) or ANDA applicant may send notice of paragraph IV certification would reduce the need for such applicants to submit written requests to use an alternate delivery method. We currently receive about 200 such requests each year and believe 95 percent of the requests, or 190 of the 200, would be unnecessary under the proposal. Assuming a request takes 30 minutes and is completed by a regulatory affairs specialist at \$91.27 per hour, this proposal would reduce costs by \$8,671 annually. Based on our experience with granting these requests, we can expand the list of acceptable delivery methods without creating costs elsewhere. This proposal might also benefit applicants that are not currently submitting written requests but would otherwise prefer to use an alternate delivery method.

We are proposing to change the required contents of the notice of paragraph IV certification. Proposed §§ 314.52(c) and 314.95(c) would require that the notice of paragraph IV certification contain a statement that the acknowledgment letter or paragraph IV acknowledgment letter has been received. Including this statement in the notice of certification would confirm that required notice was being provided in a timely fashion, facilitating compliance with and enforcement of the FD&C Act, as amended by the MMA. In addition, proposed § 314.52(c) would require that the notice include a statement that a 505(b)(2) application containing any required bioavailability or bioequivalence data has been submitted by the applicant and filed by FDA. We estimate that 7 505(b)(2) applications and 209 ANDAs are filed each year with paragraph IV certifications, and that these applications contain, on average, 3 paragraph IV certifications to listed patents. The 216 applications with paragraph IV certifications would result in 648 affected patent certifications. Based on experience with similar provisions, we estimate that a regulatory affairs specialist would spend an additional 20 minutes

on each paragraph IV certification, for 216 additional hours. The estimated cost of 216 hours at \$91.27 per hour is \$19,714.

Proposed §§ 314.52(d)(1) and 314.95(d)(1) would 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 proposed provisions, if finalized, would codify current practice and would not result in additional costs.

Proposed §§ 314.52(e) and 314.95(e) would allow a 505(b)(2) or ANDA applicant to submit one amendment for both the documentation of timely sending and receipt of notice of the paragraph IV certification. As applicants are currently required to submit two separate amendments, this provision would reduce costs. Proposed § 314.95(e) would also require the ANDA applicant to 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 7 505(b)(2) applicants and 209 ANDA applicants with paragraph IV certifications would spend 1 less hour per certification, while the cost of submitting the page from the Orange Book would be negligible. At \$91.27 per hour, the estimated cost reduction for 216 responses is \$19,714.

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). Proposed § 314.101(b)(4) would create an administrative consequence to encourage compliance with MMA by delaying the submission date of an ANDA by the number of days the applicant exceeds the statutory timeframe for providing notice. We believe almost all ANDA applicants currently

meet the 20-day deadline, but FDA currently lacks formal procedures to address instances when an applicant fails to do so. In proposing this approach, we have chosen an administrative consequence that would reinforce compliance without creating consequences inconsistent with the nature of the infraction.

We do not provide an estimate of the impact of this proposal on the timing of ANDA approvals because we cannot reliably estimate an expected size of the consequence. Almost all applicants with paragraph IV certifications (first applicants and subsequent applicants) provide notice within 20 days of receipt of FDA's paragraph IV acknowledgment letter. We expect that an administrative consequence would improve compliance. However, we have not yet needed to address a scenario in which an applicant was the first filer of an ANDA that contained a paragraph IV certification, failed to provide notice within the 20-day period, and another ANDA applicant could have been eligible for 180-day exclusivity. Based on our experience, assuming FDA receives about 200 ANDAs each year with paragraph IV certifications, and that the existence of the administrative consequence would improve current compliance levels, we assume the administrative consequence would be imposed approximately once per year.

The potential impact of the administrative consequence is highly uncertain. Delaying the ANDA submission date could delay the date of approval, but if the application is ultimately tentatively approved prior to the expiration of all patents and exclusivities, the delay could have no monetary impact. Alternatively, if the delaying applicant and another applicant submitted their ANDAs with paragraph IV certifications on the same first day and the other applicant provided timely notice, the delaying applicant could lose first applicant status and the opportunity for a period of 180-day exclusivity. The loss of benefit from losing first applicant status and 180-day exclusivity would depend on the market factors and competitive conditions

(including whether and how many additional applications would be approved sooner) but could, in theory, be in the hundreds of millions of dollars. The existence of such an administrative penalty, however, would make the failure to provide notice in that situation to be extremely unlikely.

In proposing an administrative consequence, we considered lesser consequences for failing to comply with the statutory requirement, but felt such lesser measures would not encourage compliance. We also considered a penalty where failing to meet the deadline would result in the paragraph IV certification being deemed not “lawfully maintained.” Under this approach, an ANDA applicant would certainly lose its first applicant status and an opportunity for 180-day exclusivity. We rejected this approach as the severity of the negative consequences seemed inconsistent with the nature of the infraction and beyond what was needed to enforce the MMA. We considered administrative consequences that would apply to 505(b)(2) applications, but were unable to find a mechanism that would reasonably balance the desire to improve compliance with an appropriate administrative consequence. We believe the costs associated with the proposed administrative consequence are justified by the benefits from improved enforcement of the MMA.

#### I.C.5. 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 to a newly issued patent for which patent information is timely filed by the NDA holder for the listed drug. Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii) would 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 a settlement order or consent decree with a finding of infringement. These provisions would 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 the patents that would trigger the need to revise a patent certification, nor do we know for each triggering patent, the number of 505(b)(2) and ANDA applicants that would be required to amend their certification. Based on our experience, we estimate this requirement would result in 36 and 108 instances per year in which an applicant would amend its 505(b)(2) application or ANDA to submit a revised patent certification. At 2 hours per response and \$91.27 per hour, the estimated cost of 144 responses is \$26,286.

#### I.C.6. Patent Certification Requirements for Amendments and Supplements to 505(b)(2) Applications and ANDAs

An amendment or a supplement to a 505(b)(2) application or an ANDA has 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 are proposing to revise the requirements to further ensure that applicants submitting amendments or supplements for specified types of changes to their products will 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. Proposed § 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. Proposed § 314.70(i) requires a 505(b)(2) supplement to contain a patent certification if it would add a new indication or other condition of use, or add a new strength. The applicant would be required to provide a patent certification and, if a paragraph IV notification, provide notice of the paragraph IV certification that would include the basis for the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed. This would be a new cost for 505(b)(2) applicants for certain types of amendments, but we do not have a precise estimate for how often this would occur. In general, few 505(b)(2) applications contain paragraph IV certifications. We estimate six amendments and four supplements would need to include a new certification each year, each requiring 2 hours of time from a regulatory affairs specialist. The 10 additional certifications would require 20 hours of time at \$91.27 per hour for an estimated cost of \$1,825.

Proposed §§ 314.96(d) and 314.97(c) would apply the same patent certification requirements for amendments and supplements, respectively, to ANDAs. We do not have a precise estimate for the number of amendments or supplements to ANDAs that would need to contain a new patent certification under this proposal. For ANDAs, we estimate the provision would require additional patent certifications for 95 amendments and 16 supplements to ANDAs. The 111 additional patent certifications would require 222 hours of time at \$91.27 per hour or \$20,261. Combining the estimated costs for 505(b)(2) applicants and ANDAs, the estimated cost of the proposal is \$22,087.

I.C.7. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and Amendments or Supplements to an ANDA That Reference a Different Listed Drug

Proposed §§ 314.60(e) and 314.70(h) would prohibit an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient 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.

Proposed §§ 314.96(c) and 314.97(b) would prohibit 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 would 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 the drug product for which the petitioned ANDA was submitted while the petitioned ANDA is pending. The ANDA applicant would not be permitted to amend the pending petitioned ANDA to cite the newly approved pharmaceutical equivalent as its RLD. Such a change would be required to be made in a new ANDA. Section 1101(a)(1)(A) of the MMA includes this provision to prevent applicants from strategically changing RLDs and circumventing certain intellectual property protections. If an applicant with a pending ANDA needed to identify a newly listed drug as its RLD, it would be 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 would be consistent with current practice, estimated costs are negligible.

I.C.8. Procedure for Submission of an 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 propose to revise § 314.54 to require a 505(b)(2) application to identify such a pharmaceutically equivalent drug as a listed drug relied upon. As 505(b)(2) applications typically identify a pharmaceutically equivalent drug product as a listed drug relied upon, applicants generally comply with this proposal. Any cost from this provision would be too small to reliably estimate.

#### I.C.9. 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 a 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. Proposed § 314.93 would codify current practice. There may be some small benefit associated with fewer suitability petitions that would ultimately not be granted, but any quantifiable monetized benefit would be so small as to make reliable estimation impossible.

#### I.C.10. Filing an NDA and Receiving an ANDA

This proposed rule would codify FDA's practice of sending an acknowledgment letter to notify a 505(b)(2) or ANDA applicant that its application has been filed or received, respectively. It would also repeal outdated language regarding antibiotics, clarify certain refuse-to-file provisions as applying to both NDAs and ANDAs, and simplify the wording of a current regulation. Because proposed § 314.101, if promulgated, would not differ from current practice, its impact would be negligible.

#### I.C.11. Approval of an NDA and ANDA



This proposed rule would clarify 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. The proposed revisions to § 314.105, if promulgated, would conform to current FDA practice and would result in no additional costs.

#### I.C.12. Refusal to Approve an NDA or ANDA

Proposed revisions to §§ 314.90, 314.99, 314.125, and 314.127 would codify FDA’s longstanding position that a waiver of a submission requirement for an NDA or ANDA also waives that requirement as a condition for approval. Because the proposed rule would codify FDA’s current approach, there would be no additional costs.

#### I.C.13. Date of Approval of a 505(b)(2) Application or ANDA

Proposed § 314.107(e) would expand the requirements associated with the notification of FDA of court actions and documented agreements. It is current practice for applicants to notify FDA within 10 days of a final judgment, and we receive about 100 such responses per year. By expanding the set of triggering actions, this proposal would result in more responses. We estimate that under this proposal we would receive 310 responses each year, an increase of 210 over current practice. At an estimated 30 minutes of time per notification from a regulatory affairs specialist at \$91.27 per hour, the estimated annual cost of this provision would be \$9,583.

#### I.C.14. 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. Proposed § 320.23 would codify FDA's existing practice of establishing such methods and estimated costs are negligible.

#### I.C.15. Miscellaneous Changes

This proposed rule would make several minor editorial changes to current regulations. These changes involve 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.

Table 1.--Impact Summary

Section of This Document	General Change	Annual Benefits	Annual Costs
I.C.1. Definitions	Establish definitions.		
I.C.2. Submission of Patent Information	Reduce innovator patent declaration requirements.	\$165,929 from saving 3 hours for 606 patent declarations.	
	Require submission of corrected patent information (e.g., for patent term extensions) and describe procedures for withdrawal of patents that no longer meet the statutory requirements for listing.		\$5,476 for 60 additional requests at \$91.27 each.
	More clearly defines requirements for submission of information on method-of-use patents, facilitating generic “carve-out.”	Aligns submitted patent information with innovator intellectual property protected by patent. Potentially facilitates generic entrance into the market under certain circumstances.	
I.C.3. Patent Certification	Require 505(b)(2) applicants to provide a patent certification to a pharmaceutically equivalent drug product.		\$8,225 for 2 instances requiring identification of a pharmaceutically equivalent product as a listed drug.
I.C.4. Notice of Paragraph IV Certification	Expand the list of acceptable delivery methods for 505(b)(2) and ANDA applicants providing notice, reducing the need for formal requests to FDA.	\$8,671 savings from 190 fewer requests.	
	Require 505(b)(2) and ANDA applicants to include a statement that it has received an acknowledgment letter or paragraph IV acknowledgment letter in its notice of paragraph IV certification. Requires 505(b)(2) applicants to include a statement on bioequivalence data, if appropriate.		\$19,714 for additional information in 648 certifications.
	Allow for the submission of a single amendment for both documentation of timely sending and receipt of notice of the paragraph IV certification.	\$19,714 for additional information in 216 fewer required responses.	
	Establish administrative penalties for ANDA applicants failing to provide notice of paragraph IV certification within 20 days of receipt of an acknowledgment letter or paragraph IV acknowledgment letter from FDA.	Facilitates compliance with timeframe established in MMA. Impact not quantified, as impact heavily dependent on precise circumstances.	
I.C.5. Amended Patent Certifications	Require 505(b)(2) and ANDA applicants to amend patent certifications if no longer accurate.		\$26,286 for 144 additional amendments to patent certifications.

Table 1.--Impact Summary (continued)

Section of This Document	General Change	Annual Benefits	Annual Costs
I.C.6. 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.		\$22,087 for additional certifications for 10 505(b)(2) applications and 111 ANDAs.
I.C.7. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and Amendments or Supplements to an ANDA That Reference a Different Listed Drug	Prohibit an applicant from amending or supplementing an ANDA to reference a different RLD. Instead, the applicant must submit a new ANDA.		Negligible, consistent with current practice under the statute.
I.C.8. Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication For, or Other Change From, a Listed Drug	Establish requirements for 505(b)(2) applications to identify a pharmaceutically equivalent drug as a listed drug relied upon.		Expected impact small; generally in compliance.
I.C.9. Petition to Request a Change From a Listed Drug	Clarify procedures for petitioned ANDAs.		Negligible, would codify current practice.
I.C.10. Filing an NDA and Receiving an ANDA	Clarify FDA acknowledgment letter procedures.		Negligible, would codify current practice.
I.C.11. Approval of an NDA and ANDA	Clarify definition of an approved application and procedures related to tentative approval.		Negligible, would codify current practice and address confusing language.
I.C.12. Refusal to Approve an NDA or ANDA	Clarify that a waiver of an application requirement is a waiver of an approval requirement.		Negligible, would codify current practice.
I.C.13. Date of Approval of a 505(b)(2) Application or ANDA	Revise the description of court actions relevant to the date of approval of a 505(b)(2) application or ANDA, and require submission of related documentation.		\$9,583 for 210 additional notifications.
I.C.14. Assessing Bioavailability and Bioequivalence for Drugs Not Intended to be Absorbed Into the Bloodstream	Codify statutory revisions in the regulations.		Negligible, would codify current practice.
I.C.15. Miscellaneous Changes	Editorial changes.	Would address confusing language.	Negligible.
Total Monetized Impacts		\$194,314	\$91,371

I.D. Small Business Analysis

The following analysis along with other sections of this document constitute the Agency's preliminary regulatory flexibility analysis as required under the Regulatory Flexibility Act.

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

The proposed rule applies to applicants submitting NDAs (including 505(b)(2) applications) and ANDAs and to NDA and ANDA holders. According to the Table of Small Business Size Standards, the U.S. Small Business Administration (SBA) considers pharmaceutical preparation manufacturing entities (NAICS 325412) with 750 or fewer employees to be small. Statistics on the classification of firms by employment size from the U.S. Bureau of the Census show that in 2005, at least 85 percent of pharmaceutical manufacturing entities had fewer than 500 employees and would have been considered small by SBA (Ref. 3).

We have provided monetized estimates of \$194,314 in benefits and \$91,371 in costs. These costs of this proposed rule are generally small unit costs incurred across many entities. Our estimated unit costs for all but one item are less than \$190 per unit. In table 17 of this document, we express the unit cost of an amendment to a patent certification in terms of hundredths of a percent of average establishment shipments. Excluding one item (505(b)(2) applicants providing a patent certification to a pharmaceutically equivalent drug product), there are costs of \$83,146 attributable to about 1,200 units. Some affected entities would face multiple unit costs of some type in a year, but even this circumstance would not approach a significant

impact on a substantial number of small entities. For a unit cost of \$190 to amount to 1 percent of average shipments among establishment with fewer than 5 employees, the entity would have to incur that cost more than 40 times.

This proposal would require 505(b)(2) applicants to identify a pharmaceutically equivalent drug product as a listed drug relied upon and comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for the pharmaceutically equivalent listed drug relied upon). The estimated cost of this provision is \$4,113 per instance. As shown in table 17 of this document, for firms with fewer than 5 employees, the unit cost of this provision would be less than 1 percent of average firm shipments, below a range that has been cited as a threshold for significant impacts.<sup>5</sup> For firms with 25 to 49 employees, which is a more likely lower bound for firms submitting 505(b)(2) applications, the unit cost of this provision would be less than 0.05 percent of average shipments. We do not believe such a cost constitutes a significant impact.

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

---

<sup>5</sup> 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).

Table 2.--Small Entity Characteristics and the Impact of Unit Costs Attributable to this Proposed Rule

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

## II. References

1. Bureau of Labor Statistics (BLS). 2010. Employer Costs for Employee Compensation Table 5. Private industry, by major occupational group and bargaining status (June 9, 2010 Release). Available at <http://www.bls.gov/news.release/ecec.t05.htm>.
2. Bureau of Labor Statistics (BLS). 2009. May 2009 National Industry-Specific Occupational Employment and Wage Estimates for NAICS 325400 - Pharmaceutical and Medicine Manufacturing, SOC 23-1011 Lawyers. Available at [http://www.bls.gov/oes/current/naics4\\_325400.htm#23-0000](http://www.bls.gov/oes/current/naics4_325400.htm#23-0000).
3. U.S. Department of Commerce, Bureau of the Census, Economic Census, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, Table 4, EC02-311-325412 (RV), 2002.
4. U.S. Department of Health & Human Services, “Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services,” May 2003.
5. Coase, R. H. (1960). “The Problem of Social Cost,” *Journal of Law and Economics*, 3, 1-23.



## Technical Appendix A

*The economic model described in this technical appendix identifies the major factors that may bear on the potential effects of FDA's proposal to review a proposed labeling carve-out for a 505(b)(2) application or ANDA with reference to the applicant's interpretation of the scope of the method-of-use patent. The economic model also illustrates certain conditions in which this proposal could lead to a change in outcome. This model does not include all factors that may bear on the outcome. Under the assumptions illustrated in the economic model, we examine a hypothetical situation where it would be possible to expect earlier market entry by a generic drug applicant as a result of the provision. However, the conceptual economic model does not limit this outcome only to scenarios in which the assumptions are true nor does the model require that the assumptions are necessarily true. The technical appendix describes certain conditions that can lead to various outcomes. A basic feature of the model is that different outcomes would follow from different assumptions. The statements made in this technical appendix, for purposes of the economic analysis, do not create or confer any rights for or on any person and do not operate to bind FDA or the public.*

Some patents claim a method of using a drug. Proposed § 314.53(b)(1) would more clearly align the requirements for submitting 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 must start with the use code information provided by the NDA holder (rather than doing an independent analysis of the scope of the patent) and use this information to determine whether the proposed application is seeking approval for a method of use claimed by the listed patent.

This proposed rule would explicitly require that if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder's use code must describe only the specific portion(s) of the indication or other method of use claimed by the patent. By requiring close alignment of the patent use code with the actual scope of the patent claims, the Agency would be appropriately protecting the intellectual property rights of the NDA applicant. By expressly prohibiting an overbroad description of the method(s) of use claimed by a listed patent and, in certain scenarios, proposing to review a proposed labeling carve-out for the 505(b)(2) application or ANDA with reference to the generic applicant's (rather than the NDA holder's) interpretation of the scope of the patent, the proposal is intended to facilitate removal of an unwarranted barrier to submission or approval of a 505(b)(2) application or an ANDA for uses that are not claimed by a listed patent.

Under the status quo, 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 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. For an overbroad use code that purports to cover 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 that the provision 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 initiates patent infringement litigation, then the generic applicant can file a counterclaim seeking to correct the use code. If the counterclaim is successful, the generic applicant can amend its application to revise its patent certification 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.

Under the proposed rule, if, despite the enhanced instructions for the content of a use code, an NDA holder submits an overbroad use code and other criteria are met, a generic applicant would not be required to file a counterclaim in a paragraph IV lawsuit (as described in scenario (3)) in order to align its labeling carve-out more closely to the actual scope of the patent. Instead, an applicant could propose a narrower labeling carve-out than the use code would suggest and FDA would review the proposed labeling carve-out and determine whether the drug remains safe and effective for the remaining non-protected conditions of use with reference to the generic applicant's interpretation of the approved conditions of use that are within the scope of the patent, not with reference to the use code that the NDA holder provided. By removing certain barriers to use of the existing statutory mechanism for carving out labeling claimed by a patent, this provision is intended to prevent instances where an overbroad use code effectively causes a delay in generic entry because the generic applicant is limited as a practical matter to scenarios (2) and (3) - submitting a paragraph III certification that would delay approval until patent expiry or submitting a paragraph IV certification, respectively. The latter option may result in the generic applicant getting sued for patent infringement and may provide an opportunity for that applicant to file a counterclaim to correct the use code which could result in market entry before patent expiry ("early market entry").

To quantify the potential effects of this provision, 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 this provision. 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.

Aside from information obtained from reported court decisions, we do not know the likelihood under the existing regulations that an NDA holder would submit an overbroad use code that would explicitly not be permitted under this proposal (see, e.g., Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670 (2012)). 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 scope of the patent would make it possible for generic applicants to submit a statement that the method-of-use patent does not claim a use for which the applicant is seeking approval and a permissible carve-out (under scenario (1)) instead of a paragraph III certification or a paragraph IV certification (under scenarios (2) and (3), respectively).

While we are unable to precisely quantify the impact, we consider a model based on the Coase theorem (Ref. 5), specifically in the context of baseline scenarios (2) and (3), to identify the major determinants that affect whether this provision would reduce delays in generic drug entry and to derive general conditions in which this provision could potentially bring about a different outcome in terms of avoiding litigation. In our conceptual framework, we examine the decision faced by the generic firm on whether to submit a Paragraph III certification or a Paragraph IV certification (rather than a labeling carve-out) in the simple case of an RLD with only one listed patent that claims only a method of use and for which the use code is overbroad and describes the patent as claiming all approved methods of using the drug. We examine how this decision is affected by the proposal, in this circumstance, if FDA finds that it cannot determine the scope of the patent based on the use code and approved labeling and the NDA holder has confirmed the accuracy of the patent information. Under the proposal in this circumstance, the generic applicant has the option of proposing a labeling carve-out based on its own interpretation of the scope of the patent in order to utilize the existing statutory mechanism which permits an applicant to not seek approval for a patented method of use (and to carve such patented use out of the labeling for which it seeks approval). Similarly, we model the decision faced by the NDA holder on whether to initiate patent infringement litigation when notified of a Paragraph IV certification and whether to initiate patent infringement litigation after generic drug approval if the generic firm enters the market with a labeling carve-out based on the generic applicant's interpretation of the scope of the patent. We assume that both NDA holder and generic applicant solve for their profit maximization problem in determining their best strategies, which implies that the expected private benefit from an action outweighs its expected private cost.

To be concrete, let us assume that if the generic applicant gains approval via the new “carve-out” approach and enters the market earlier (i.e., before patent expiry), its expected profit would be  $\pi_G^E$  and the NDA holder's expected profit would be  $\pi_N^E$ . Let us assume that if the generic applicant uses the “Paragraph III” mechanism its expected profit would be equal to its expected profit from waiting until patent expiry,  $\pi_G^D$ , and the NDA holder's expected profit would be  $\pi_N^D$ . For the purposes of this analysis, we make the simplifying assumption that the generic applicant's and the NDA holder's expected litigation costs are  $C_G$  and  $C_N$ , respectively, for both litigation brought before generic approval (based on a paragraph IV certification to a patent based on an overbroad use code that cannot be carved out) and litigation brought after approval (based on a carve-out that the NDA holder does not agree is broad enough to prevent patent infringement). We also make the simplifying assumption that regardless of the type of litigation, the probability that the generic firm prevails (i.e., achieves the ability to enter the market before patent expiry) and the NDA holder loses is  $P_G^W$ , while the probability that the

generic firm loses (and NDA holder succeeds in delaying generic entry until patent expiry) is  $(1 - P_G^W)$ .<sup>6</sup>

One key distinction that could affect the generic firm’s incentive to submit a paragraph IV certification (instead of proposing an alternative carve-out based on its interpretation of the scope of the patent) is the possibility for the generic firm to receive 180-day exclusivity if it is the first generic applicant to submit a substantially complete application that contains and for which it lawfully maintains a paragraph IV certification (“first applicant”). However, it is important to note that 180-day exclusivity would only delay approval of another generic drug application that also contained a paragraph IV certification. It would not block approval of a competing generic drug application where the applicant sought to enter the market with a labeling carve-out based on its interpretation of the scope of the patent; indeed, the competitor generic drug applicant could enter the market earlier than the first applicant if the first applicant’s paragraph IV certification resulted in patent infringement litigation. In non-Paragraph IV patent infringement litigation, the potential granting of the 180-day generic market exclusivity to the first generic applicant would not be a possible outcome. To model this, we define the generic applicant’s potential payoff from the 180-day exclusivity award,  $E \geq 0$ , as the difference between its profit from prevailing in Paragraph IV litigation, and its profit from prevailing in non-Paragraph IV patent infringement litigation. We assume if a Paragraph IV-related litigation resolves in favor of the generic applicant, its gain would be  $\pi_G^L + E - C_G$ . If the generic applicant prevails in a non-Paragraph IV patent infringement suit, we assume its gain would be  $\pi_G^L - C_G$ , implying that when there is no potential for additional gain from the 180-day exclusivity award, or  $E = 0$ , the expected profit from winning would be the same in either type of litigation. We assume that if the generic applicant loses the patent infringement litigation it would wait to enter the market when the patent expires and therefore it would receive the difference between its profit from waiting until patent expiry and the cost of litigation or  $\pi_G^D - C_G$ . Therefore, the generic applicant’s expected value associated with litigation can be expressed as  $P_G^W(\pi_G^L + E - C_G) + (1 - P_G^W)(\pi_G^D - C_G)$ , where we assume  $\pi_G^E \geq \pi_G^L \geq \pi_G^D \geq 0$ .

The second distinction that could affect the incentive to litigate relates to the 30-month stay of approval provision. When an NDA holder initiates patent infringement litigation in response to notice of a paragraph IV certification within the statutory timeframe, FDA approval of the generic firm’s application is automatically stayed for up to 30 months while the litigation is pending. In the absence of a paragraph IV certification *and* initiation of patent infringement litigation within the statutory timeframe, there would not be an automatic 30-month stay of approval based on the paragraph IV certification. However, once a generic applicant has been approved it could be enjoined from marketing during the pendency of or after losing a non-Paragraph IV patent infringement suit.

---

<sup>6</sup> We note that the probability that the generic firm prevails in patent infringement litigation (and the NDA holder loses) may be greater if the generic firm enters the market with a labeling carve-out based on the generic applicant’s interpretation of the scope of the patent than if the generic firm submits a paragraph IV certification and proposed labeling that includes the patented method of use. Holding all else constant, a higher relative probability of the generic winning would increase the attractiveness of the “carve-out” option for the generic and decrease the attractiveness of patent infringement litigation from the NDA holder’s perspective.

The 30-month stay provision associated with a Paragraph IV-related litigation may incentivize the NDA holder to initiate patent infringement litigation by prolonging the period without generic competition. To allow for differences in the expected payoff attributable to the 30-month stay, we define  $S \geq 0$  as the difference between the NDA holder's expected value from Paragraph IV and its expected value from non-Paragraph IV patent infringement litigation. We assume that if the NDA holder loses the non-Paragraph IV litigation its profit would be  $\pi_N^L - C_N$ , but if it were to lose in a Paragraph IV challenge its profit would be  $\pi_N^L + S - C_N$ . We assume that the NDA holder's profit from winning the Paragraph IV litigation would be no different from its profit winning the non-Paragraph IV litigation, in which it receives the maximum profit under generic entry at patent expiry minus its litigation costs. Therefore, we can express the NDA holder's expected value from litigation as  $(1 - P_G^W)(\pi_N^D - C_N) + P_G^W(\pi_N^L + S - C_N)$ , which implies that when there is no incremental gain associated with the 30-month stay provision, or  $S = 0$ , there would be no difference in the expected profit in either types of litigation. We also assume that  $\pi_N^D \geq \pi_N^L \geq \pi_N^E \geq 0$ .

In the context of scenario (2), if the generic applicant used the Paragraph III mechanism when the only other option was the Paragraph IV mechanism, we know that from the perspective of the generic applicant, the expected cost of litigation outweighs the expected payoff or  $C_G > P_G^W(\pi_G^L - \pi_G^D + E)$ . In the context of scenario (3), if Paragraph IV-related litigation occurred, it must be true that the generic applicant's and the NDA holder's respective expected payoff from litigation each outweighs its expected cost. This condition yields the following inequalities, (Eq. 1)  $C_G \leq P_G^W(\pi_G^L - \pi_G^D + E)$  and (Eq.2)  $C_N \leq (1 - P_G^W)(\pi_N^D - \pi_N^L - S) + (\pi_N^L - \pi_N^E + S)$ . Note, as mentioned previously, we are referring to situations in which there would have been a delay in the absence of the rule, where only Paragraph III or Paragraph IV routes are available and the use of the Paragraph IV mechanism would have resulted in litigation. If the generic applicant had been able to successfully carve out the patented method-of-use without litigation or if there was no Paragraph IV-related litigation, we assume there would not have been a delay in the first place.

In order for there to be a reduction in delay attributable to this provision, it would be a necessary condition that it is in the best interest of the generic applicant to use the new "carve-out" approach, rather than to use other mechanisms available in the absence of this provision. If the generic applicant would have previously used the "Paragraph IV mechanism," in order for it to choose the new carve-out mechanism the generic applicant's expected profit from earlier entry using the "carve-out" mechanism would have to outweigh its expected value from the "Paragraph IV" mechanism, or  $\pi_G^E > P_G^W(\pi_G^L + E - C_G) + (1 - P_G^W)(\pi_G^D - C_G)$ . This implies that the generic applicant's expected cost of Paragraph IV litigation must exceed its expected incremental gain from such litigation, which yields the following inequality that must be satisfied (Eq. 3)  $C_G > P_G^W(\pi_G^L - \pi_G^D + E) - (\pi_G^E - \pi_G^D)$ . Satisfying both conditions expressed in (Eq. 1) and (Eq. 3) implies that in order for the generic applicant to be expected to use the new carve-out mechanism, the generic applicant's net gain from using the Paragraph IV mechanism must be bounded by its net gain from earlier entry using the "carve-out" option and zero or  $(\pi_G^E - \pi_G^D) > P_G^W(\pi_G^L - \pi_G^D + E) - C_G \geq 0$  (Eq. 4).

In addition to the inequality conditions for the generic applicant specified in (Eq. 4), in order for there to be an outcome of no litigation when the generic applicant uses the new "carve-

out” mechanism, it would be necessary that the NDA holder’s expected profit under earlier generic competition outweighs its expected value from non-Paragraph IV patent infringement litigation, or  $\pi_N^E > (1 - P_G^W)(\pi_N^D - C_N) + P_G^W(\pi_N^L - C_N)$ . This condition implies that the NDA holder’s expected cost of litigation exceeds its expected payoff from litigation, or  $C_N > (1 - P_G^W)(\pi_N^D - \pi_N^L) + (\pi_N^L - \pi_N^E)$  (Eq. 5). Satisfying both conditions expressed in (Eq. 2) and (Eq. 5) implies that although the NDA holder’s expected cost of litigation must be greater than its expected gain from litigation, the difference is bounded by the gain attributable to the 30-month stay provision, or  $0 < C_N - [(1 - P_G^W)(\pi_N^D - \pi_N^L) + (\pi_N^L - \pi_N^E)] \leq P_G^W S$  (Eq. 6).

Taken together, the conditions summarized in (Eq. 4) and (Eq. 6) illustrate the types of cases in which we could expect this provision to reduce instances of litigation and to reduce delays in generic competition. Although there is uncertainty in determining the likelihood that these conditions would be true, several observations follow from the theoretical results. From the condition in (Eq. 4), we would expect that if there were no associated gain from exclusivity, or  $E = 0$ , then it would always be preferred for the generic applicant to use the “carve-out” mechanism. Moreover, if the generic firm’s gain from earlier entry using the “carve-out” mechanism is the same as its gain from prevailing in Paragraph IV litigation, or  $\pi_G^E = \pi_G^L$ , and the probability of the generic winning its Paragraph IV litigation (i.e., achieving market entry before patent expiry) is high, unless its net gain from exclusivity is greater than the net gain from the “carve-out” mechanism, we would expect that the generic applicant would still prefer the “carve-out” mechanism. From the condition in (Eq. 6), we expect that the NDA holder would be unlikely to initiate patent infringement litigation under the rule unless the patent infringement litigation was initiated in response to a notice of a paragraph IV certification and the NDA holder expected to benefit from a 30-month stay. This also implies that in cases where there was no additional gain generated by the 30-month automatic stay, that is  $S = 0$ , there would be no change NDA holder’s decision to engage in litigation because the incentives faced by the NDA holder would be the same.

In other words,  $E > 0$  provides a strong incentive for generic applicants to use the paragraph IV mechanism, even if the “carve-out” mechanism becomes available. It is possible, however, that the  $E > 0$  incentive may be offset by a higher probability of realizing early-entry profit,  $\pi_G^E$ , rather than litigation-outcome profit,  $\pi_G^L$ . This outcome would be expected if  $E$  is relatively small and if the removal of stay profit  $S$  is large enough to change the NDA holder’s litigation decision (from claiming patent infringement in response to the generic applicant using the paragraph IV mechanism to not claiming patent infringement in response to the generic applicant using the “carve-out” mechanism).  $E$  and  $S$  are correlated, however, so the conditions under which the “carve-out” mechanism created by the proposed rule would reduce delays in market entry by generics (that is,  $E$  being small and  $S$  being big) are unlikely to occur simultaneously. As we are unable to empirically test the predictions of the model, we welcome comment and data that would allow us to quantify the impacts of this provision.