



Making American Healthcare More Affordable

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**VIA MESSENGER**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
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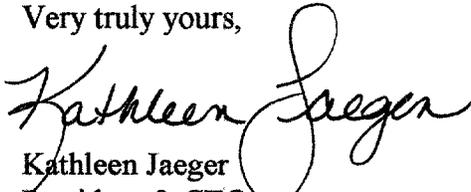
**Re: Comments on Behalf of GPhA Regarding FDA's Request for  
Comments Concerning What, If Any, Regulatory Provisions  
Are Needed In Light Of Recent Statutory Changes  
(Docket No. 2004N-0087)**

Dear Sir or Madam:

On behalf of the Generic Pharmaceutical Association ("GPhA"), we submit the attached in response to FDA's request for comments regarding what additional regulatory provisions, if any, are needed in light of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. *See* 69 Fed. Reg. 9982 (Mar. 3, 2004).

Should you have any questions regarding these comments, please do not hesitate to contact me. We appreciate the opportunity to comment on this important issue.

Very truly yours,

  
Kathleen Jaeger  
President & CEO

Enclosure

2004N-0087

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**Comments on Behalf of GPhA Regarding  
FDA's Request for Comments Concerning What, If Any, Regulatory  
Provisions Are Needed In Light Of Recent Statutory Changes  
(Docket No. 2004N-0087)**

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") altered the legal landscape governing FDA approval of generic drug products, including the private patent litigation often involved in the launch of such drug products. Congress passed the MMA for the purpose of increasing the public's access to less expensive generic drug products. It did so by enacting provisions designed, among other things, to curb many of the abuses that brand companies had developed over the years to slow, and in some cases prevent altogether, the launch of generics. In this time of skyrocketing healthcare costs, the public sorely needed such legislation.

The new statutory provisions have rendered some current regulations obsolete, while leaving others in need of modification. The MMA provisions will, therefore, require the Agency to revisit some of its existing regulations. The following addresses some of those provisions and, where appropriate, provides the Agency with suggested modifications.<sup>1</sup> Further, the Agency should also consider adopting some additional regulations in order to ensure that the MMA accomplishes Congress' goal of increasing the public's access to lower-priced generic drug products.

Finally, many companies, organizations, and groups likely will offer comments on the MMA's impact on the Agency's regulatory scheme. Given the importance of the MMA provisions, GPhA will review these submissions carefully and offer responses so that the Agency can ensure that its implementing regulations complement, not hinder, Congress' goal of increasing the public's access to less-expensive, life saving drugs.

## **I. MODIFICATIONS TO EXISTING REGULATIONS**

As the Agency is aware, the MMA contains effective date provisions for all of the statutory changes. Generally speaking, whether one or more of the revised MMA provisions apply to a particular ANDA depends upon when the application and/or relevant patent information was submitted to the Agency. Given the nature of how the effective date provisions operate, the changes made to the current regulatory scheme will apply only to certain applications and will not apply across the board to all pending ANDAs. In proposing the changes discussed below, we have included prefatory language indicating the applications to which the provisions apply. For the Agency's convenience, we have also included citations to the relevant effective date provisions.

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<sup>1</sup> These comments focus on the regulations relating to ANDAs. Where applicable, however, this submission references the corresponding regulations for 505(b)(2) applications. Additionally, for the Agency's convenience, when suggesting changes to existing regulations, we have underlined the new language.

(1) **21 C.F.R. § 314.53(f)**

Presently, the Agency will not remove disputed patent information unless the NDA holder withdraws or amends its patent information. Under the MMA, however, ANDA applicants now have the ability to bring counterclaims seeking an order requiring the NDA holder to correct or delete patent information. *See* MMA § 1101(a)(2)(C) (codified at 21 U.S.C. § 355(j)(5)(C)(ii)). The regulatory scheme should, therefore, expressly require an NDA holder to correct or delete patent information in response to a court order requiring such action. Proposed language would include:

<Text of subsection (f) effective for any proceeding completed prior to December 8, 2003>

[Current text of § 314.53(f)]

<Text of subsection (f) effective for any proceeding pending on or after December 8, 2003><sup>2</sup>

(f) Correction of patent information errors.

(1) If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. . . . The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Subject to paragraph (2) of this section, unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. . . .

(2) A new drug application holder that is required by court order to amend, correct, withdraw or otherwise modify patent information must submit a copy of that order to the agency within 10 days of the entry of the order. The applicant must, at that same time, change its patent information in accordance with the terms of that order.

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<sup>2</sup> *See* MMA § 1101(c)(1).

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**(2) 21 C.F.R. §§ 314.95(b) and (d)**

Currently, this regulation addresses the sending of the statutorily-required notice letter to the NDA-holder and patentee. Now, however, the MMA contains provisions expressly addressing when an ANDA applicant must provide the required notice letter, both when submitting its application initially and when amending or supplementing an existing application. *See* MMA § 1101(a)(1) (codified at 21 U.S.C. §§ 355(j)(2)(B)(ii)(I)-(II)). At a minimum, the first sentence of § 314.95(b) must be changed to reflect the new statutory timing requirements. Proposed language for the first sentence of § 314.95(b) would include:<sup>3</sup>

<Text of subsection (b) effective for certifications made under 505(j)(2)(A)(iv) submitted prior to August 18, 2003>

[Current text of § 314.95(b)]

<Text of subsection (b) effective for certifications made under 505(j)(2)(A)(iv) submitted on or after August 18, 2003><sup>4</sup>

(b) Sending the notice. The applicant shall send the notice required by paragraph (a) of this section not later than 20 days after the date of the postmark on the notice it receives from FDA stating that its abbreviated new drug application is sufficiently complete to permit a substantive review. . . .

The Agency will also need to amend § 314.95(d), which governs amending an application to include a patent certification in light of § 355(j)(2)(B)(II).<sup>5</sup> Proposed language would include:

<Text of subsection (d) effective for certifications made under 505(j)(2)(A)(iv) submitted prior to August 18, 2003>

[Current text of § 314.95(d)]

<Text of subsection (d) effective for certifications made under 505(j)(2)(A)(iv) submitted on or after August 18, 2003><sup>6</sup>

(d) Amendment to an abbreviated application. If an abbreviated application is amended to include the certification described in

<sup>3</sup> Section 314.52(b) requires similar modifications.

<sup>4</sup> *See* MMA § 1101(c)(2).

<sup>5</sup> Section 314.52(d) requires similar modifications.

<sup>6</sup> *See* MMA § 1101(c)(2).

§ 314.94(a)(12)(i)(A)(4), the applicant shall send the notice required by paragraph (a) of this section at the time at which the applicant submits the amendment, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment to the application.

**(3) 21 C.F.R. §§ 314.101(b)(1) and (b)(2)**

Section 314.101(b)(1) states, in pertinent part: “Receipt of an abbreviated new drug application means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review.” The MMA defines a “substantially complete application” as “an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).” MMA § 1102(a)(1) (codified at 21 U.S.C. § 355(j)(5)(B)(iv)(II)(cc)). The Agency should modify § 314.101(b)(1) to make clear that its determination that an ANDA may be filed is a determination that the application is a “substantially complete application” under the MMA. Suggested language would include:

<Text of subsection (b)(1) effective for applications for a listed drug for which a paragraph IV certification was made before December 8, 2003>

[Current text of § 314.101(b)(1)]

<Text of subsection (b)(1) effective for applications filed after December 8, 2003 for a listed drug for which a paragraph IV certification was made before December 8, 2003><sup>7</sup>

An abbreviated new drug application will be reviewed after it is submitted to determine whether the abbreviated application may be received. Receipt of an abbreviated new drug application means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review and contains all the information required by paragraph 505(j)(2)(A).

Additionally, § 314.101(b)(2) states that the Agency will “notify the applicant in writing” once it accepts an ANDA for filing. As discussed above, ANDA applicants must now serve the notice letter required by § 355(j)(2)(B) “not later than 20 days after the date of the postmark on the notice” it receives from FDA. MMA § 1101(a)(1) (codified at 21 U.S.C. § 355(j)(2)(B)(ii)(I)). The Agency’s regulations should be amended to state that its written notification of filing will be sent via a postmarked document. Proposed language would include:

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<sup>7</sup> See MMA § 1102(b)(1).

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“the agency will receive the abbreviated new drug application and notify the applicant in writing via a postmarked notice.” This regulatory change would apply to a certification made under § 355(j)(2)(A)(iv) submitted on or after August 18, 2003 in an ANDA or in an amendment or supplement to an ANDA. *See* MMA § 1101(c)(2).

**(4) 21 C.F.R. § 314.107**

The MMA will require the Agency to make several changes to the approval regulations of § 314.107. This is true for ANDAs governed by the MMA provisions, and for those applications governed by the pre-MMA Hatch-Waxman statutory scheme.

**(a) § 314.107(b)(3)**

The new approval provisions of § 355(j)(5)(B)(iii) will require the Agency to make changes to § 314.107(b)(3). *See* MMA § 1101(a)(2)(A)(ii)(I) (codified at 21 U.S.C. §§ 355(j)(5)(B)(iii)(I)-(IV)). Some of those changes are immediate, while others will apply only to ANDAs governed entirely by the MMA.

First, the introductory clause of § 355(j)(5)(B)(iii) makes clear that there is a strict limitation on the availability of 30-month stays. An NDA holder can obtain a 30-month stay only on those patents listed in the Orange Book prior to the initial *submission* of the relevant ANDA. Thus, for most ANDAs there will never be more than a single 30-month stay (based on those patents listed at the time of initial submission). *See* MMA § 1101(a)(2)(A)(ii) (codified at 21 U.S.C. § 355(j)(5)(B)(iii)). Thus, the approval provision of § 314.107(b)(3)(1)(A) needs to be amended to reflect the fact that not every paragraph IV certification results in a 30-month stay.

Suggested language follows:

<Text of subsection (b)(3)(i)(A) effective for patent information submitted to FDA before August 18, 2003>

[Current text of § 314.107(b)(3)(i)(A)]

<Text of subsection (b)(3)(i)(A) effective for patent information submitted to FDA on or after August 18, 2003><sup>8</sup>

(b)(3)(i)(A) Except as provided in paragraphs (b)(3)(ii), (b)(3)(iii), and (b)(3)(iv) of this section, if, with respect to patents for which required information was submitted under section 314.53 before the date on which the application was originally submitted to FDA (excluding an amendment

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<sup>8</sup> *See* MMA § 1101(c)(3).

or supplement to the application), the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt by the patent owner of the notice of certification from the applicant under § 314.52 or § 314.95, approval may be made effective 30 months after the date of the receipt of the notice of certification by the patent owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

....

Second, in addition to the modifications discussed immediately above relating to § 314.107(b)(3)(A), the following changes are necessary based upon the amendments made to the approval provisions of §§ 355(j)(5)(B)(iii)(I)-(IV). See MMA § 1101(a)(2)(A)(ii)(II). A side-by-side of the suggested changes follows:

Current Language	Proposed Language
<Text of subsections (b)(3)(ii) through (iv) effective for applications for a listed drug for which a paragraph IV certification was made before December 8, 2003>	<Text of subsections (b)(3)(ii) through (v) effective for applications filed after December 8, 2003 for a listed drug for which a paragraph IV certification was made before December 8, 2003> <sup>9</sup>
(b)(3)(ii) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters judgment;	(b)(3)(ii) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the <u>district court decides</u> that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date <u>that the district court enters judgment reflecting the decision or the date of a settlement order or consent decree signed and entered by the district court stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed;</u>

<sup>9</sup> See MMA § 1101(c)(1).

Current Language	Proposed Language
<p>(b)(3)(iii) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court issues a final order or judgment that the patent has been infringed, approval may be made effective on the date the court determines that the patent will expire or otherwise orders; or</p>	<p>(b)(3)(iii) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the <u>district court decides</u> that the patent has been infringed:</p> <p><u>(A) if the judgment is appealed, approval is effective on the date on which the court of appeals decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement, invalidity, or unenforceability) or the date a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed;</u>  <u>or</u></p> <p><u>(B) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date the district court determines that the patent will expire or otherwise orders; or</u></p>
<p>(b)(3)(iv) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters a final order or judgment that the patent is invalid, unenforceable, or not infringed.</p>	<p>(b)(3)(iv) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid, unenforceable, or not infringed, approval may be made effective <u>as provided in paragraph (b)(3)(ii).</u></p>
	<p><u>(b)(3)(v) If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent has been infringed, approval may be made effective as provided in paragraph (b)(3)(iii)(B).</u></p>
<p>(b)(3)(v) In order for an approval to be made effective under paragraph (b)(3) of this section, the applicant must receive an approval letter from the agency indicating that the application has received final approval. Tentative approval of an application does not constitute “approval” of an application and cannot, absent a final approval letter from the agency, result in an effective approval under paragraph (b)(3) of this section.</p>	<p>[renumber as (b)(3)(vi)]</p>

**(b) § 314.107(b)(4)**

The fact that there is generally no more than a single 30-month stay also means that the Agency should make changes to § 314.107(b)(4). Specifically, because not every paragraph IV certification results in a 30-month stay, it must be clear that the approval provisions of § 314.107(b)(3) apply only to paragraph IV certifications which did, in fact, trigger a 30-month stay period. Proposed language follows:

<Text of subsection (b)(4) effective for patent information submitted to FDA before August 18, 2003>

[Current text of § 314.107(b)(4)]

<Text of subsection (b)(4) effective for patent information submitted to FDA on or after August 18, 2003><sup>10</sup>

(b)(4) Multiple certifications. If the applicant has submitted certifications under § 314.50(i) or § 314.94(a)(12) for more than one patent, the date of approval will be calculated for each certification, and the approval will become effective on the last applicable date as determined under paragraph (b)(3).

**(c) § 314.107(c)(1)**

The changes MMA made to the generic exclusivity provisions will require the Agency to make several changes to this regulatory provision. For ANDAs governed by the pre-December 8, 2003 statutory changes, the legislation changes the Agency's current interpretation of "decision of a court" for purposes of determining when generic exclusivity under § 355(j)(5)(B)(iv)(II) is triggered. Specifically, the legislation changes the "court decision" triggering exclusivity from a district court decision to the decision of a court from which no appeal has been or can be taken. This change is immediately effective for any 180-day exclusivity period not triggered prior to December 8, 2003:

(3) DECISION OF A COURT WHEN THE 180-DAY EXCLUSIVITY PERIOD HAS NOT BEEN TRIGGERED – With respect to an application filed before, on, or after the date of the enactment of this Act for a listed drug for which a certification under section 505(j)(2)(A)(vii)(IV) of that Act was made before the date of the enactment of this Act and for which neither of the events described in subclause (I) or (II) of section 505(j)(5)(B)(iv) of that Act (as in effect on the day before the date of the

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<sup>10</sup> See MMA § 1101(c)(3).

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enactment of this Act) has occurred on or before the date of the enactment of this Act, the term “decision of a court” as used in clause (iv) of section 505(j)(5)(B) of that Act means a final decision of a court from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken.

MMA § 1102(b)(3). The Agency initially defined “court decision” in § 314.107(e). However, because the new definition of “decision of a court” applies only to triggering exclusivity, and does not alter the definition of “court” for approval purposes under § 355(j)(5)(B)(iii), we suggest adding the definition of “decision of a court” to § 314.107(c).

For ANDAs filed after December 8, 2003 for listed drugs for which no paragraph IV certification has been made prior to December 8, 2003, § 314.107(c)(1) must also be changed to reflect the elimination of the court decision trigger and the new statutory definition of “first applicant.” See MMA § 1102(a)(1) (codified at 21 U.S.C. §§ 355(j)(5)(B)(iv)(I), (II)(bb)).

<Text of subsection (c)(1) effective for applications for a listed drug for which a paragraph IV certification was made, and for which generic exclusivity had not begun to run, before December 8, 2003><sup>11</sup>

(1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

- (i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or
- (ii) The date of a final decision of a court from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken, holding the relevant patent invalid, unenforceable, or not infringed.

<Text of subsection (c)(1) effective for applications filed after December 8, 2003 for a listed drug for which a previous paragraph IV ANDA was filed before December 8, 2003><sup>12</sup>

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<sup>11</sup> See MMA § 1102(b)(3).

If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that a listed patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than the date that is 180 days after the first commercial marketing of the drug product, including the commercial marketing of the listed drug, by any first applicant.

**(d) § 314.107(c)(2)**

Current § 314.107(c)(2) defines “applicant submitting the first application” and “substantially complete.” The MMA expressly includes definitions for these phrases. *See* MMA § 1102(a)(1) (codified at 21 U.S.C. §§ 355(j)(5)(B)(iv)(II)(bb), (cc)). Thus, this regulatory provision can be eliminated. If the Agency wishes for some reason to nevertheless maintain this particular regulatory provision, it must be amended to reflect the new statutory definitions of “first applicant” and “substantially complete.” Suggested language includes:

<Text of subsection (c)(2) effective for applications for a listed drug for which a paragraph IV certification was made before December 8, 2003>

[Current text of § 314.107(c)(2)]

<Text of subsection (c)(2) effective for applications filed after December 8, 2003 for a listed drug for which a paragraph IV certification was made before December 8, 2003><sup>13</sup>

For purposes of paragraph (c)(1) of this section the term “first applicant” means an applicant that, on the first day on which a substantially complete application containing a certification described in 505(2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in 505(2)(A)(vii)(IV) for the drug. A “substantially complete application” means an application that on its face is sufficiently complete to permit a substantive review and contains all the information required by 505(2)(A).

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<sup>12</sup> See MMA § 1102(b)(1).

<sup>13</sup> See MMA § 1102(b)(1).

**(e) § 314.107(c)(3)**

This provision, sometimes called the “active pursuit” provision, allows the Agency to approve subsequent applicants if the first applicant “is not actively pursuing approval of its abbreviated application.” This provision should be deleted in light of the new “failure to obtain tentative approval” forfeiture provision. *See* MMA § 1102(a)(2) (codified at 21 U.S.C. § 355(j)(5)(D)(i)(IV)). That forfeiture provision expressly addresses when generic exclusivity can be eliminated based upon an applicant’s progress before the Agency.

**(f) § 314.107(c)(4)**

This regulation should be modified to take into account that first commercial marketing includes marketing of the listed drug. *See* MMA § 1102(a)(1) (codified at § 355(j)(5)(B)(iv)(I)). Suggested language includes:

<Text of subsection (c)(4) effective for applications for a listed drug for which a paragraph IV certification was made before December 8, 2003>

[Current text of § 314.107(c)(4)]

<Text of subsection (c)(4) effective for applications filed after December 8, 2003 for a listed drug for which a paragraph IV certification was made before December 8, 2003><sup>14</sup>

(4) For purposes of paragraph (c)(1)(i) of this section, the applicant submitting the first application shall notify FDA of the date that it commences commercial marketing of its drug product, or if applicable, the commercial marketing of the listed drug. Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product (including the listed drug), except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder. If an applicant does not promptly notify FDA of such date, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing.

**(h) § 314.107(f)(2)**

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<sup>14</sup> *See* MMA § 1102(b)(1).

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Presently, this provision requires an ANDA applicant to immediately notify the Agency if suit is commenced within the 45-day clock provided by statute. Now that there are limitations on the availability of 30-month stays, such information need only be submitted as to suits which trigger a 30-month stay. Suggested language for the revised portion of this regulation includes:

<Text of subsection (f)(2) effective for patent information submitted to FDA on or after August 18, 2003>

[Current text of § 314.107(f)(2)]

<Text of subsection (f)(2) effective for patent information submitted to FDA on or after August 18, 2003><sup>15</sup>

(2) With respect to patents for which required information was submitted under section 314.53 before the date on which the application was originally submitted to FDA (excluding an amendment or supplement to the application), the abbreviated new drug applicant or the 505(b)(2) applicant shall notify FDA immediately of the filing of any legal action filed within 45 days of receipt of the notice of certification. . . .

**(5) 21 C.F.R. § 320.1(a)**

This regulation contains a definition of “bioavailability.” However, the MMA now contains an express definition of that term. *See* MMA § 1103(a)(1) (codified at 21 U.S.C. § 355(j)(8)(A)(i)). Section 320.1(a) should be modified to reflect that statutory definition. Suggested language includes:

(a) Bioavailability means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

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<sup>15</sup> *See* MMA § 1101(c)(3).

## II. ADDITIONAL REGULATORY PROVISIONS

### (1) The So-Called “Bundling” Provision

MMA Section 1101(a)(1)(B) added a new provision to Hatch-Waxman that purports to limit the circumstances under which an ANDA applicant may amend or supplement its ANDA. This provision states:

(D)(i) An [ANDA] applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after the date of the enactment of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the Secretary shall issue guidance defining the term ‘listed drug’ for purposes of this subparagraph.

MMA § 1101(a)(1)(B) (codified at 21 U.S.C. § 355(j)(2)(D)).

The key term in this new statutory provision, “listed drug,” is not defined in either the MMA nor existing provisions of the FDCA. Rather than create a statutory definition, Congress included a provision requiring FDA to issue guidance defining the term “listed drug” within 60 days of enactment. 21 U.S.C. § 355(j)(2)(D)(iii). Congress was acutely aware of, and concerned about, the potential for misinterpretation and abuse of these so-called “bundling” provisions, and accordingly, the Conference Committee report included strong language explaining that the Congressional intent was to simply codify the previously existing FDA practices with respect to what variations to a drug product may be combined within a single drug application:

In including this provision, Congress does not intend this provision to alter current U.S. Food and Drug Administration’s (“FDA”) practice regarding acceptance of supplements to approved new drug applications (“NDAs”), or amendments and supplements to pending and approved abbreviated new drug applications (“ANDAs”). Instead, Congress intends this provision to reflect the FDA’s current practice regarding those changes and variations to both innovator and generic drugs that may be approved under amendments and supplements to previously filed NDAs and

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ANDAs, and expects the Agency to maintain its current policy in designating “listed drugs.”

MMA, House Report 108-391 at 835 (Nov. 21, 2003).

In addition, the Conference Report explained that the bundling provision must *not* be interpreted in a way that would force ANDA applicants to file new ANDAs that would subject them to new or multiple 30-month stays:

*The single 30-month stay provisions are a centerpiece of this legislation, allowing lower-priced generic products to enter the market more quickly. As a result, this provision must not be construed as requiring an ANDA applicant to file a new application where, before its enactment, the applicant would have been allowed to file an amendment or supplement to an existing application. Such a construction would run directly contrary to Congress’ intent.*

House Report 108-391 at 835-836 (emphasis added).

Thus, the task facing FDA is to develop and publish a guidance document that defines the term “listed drug” in a way that continues the Agency’s current practices without creating an unintended opening for anticompetitive abuse of the generic drug approval process, and in particular, the new limitations on 30-month ANDA approval stays. To date, FDA has not issued the required Guidance on this issue. When doing so, the Agency must assure that the Guidance:

- Facilitates the most cost-effective and timely approval of generic drug products by providing ANDA applicants with as much latitude as possible to develop, and modify, products that are therapeutically equivalent to a brand-name counterpart, but which may differ in ways that do not affect the safety or efficacy of the generic product.
- Preserves Congress’ intent to end the possibility of multiple successive 30-month stays of ANDA approval by adopting a definition of “listed drug” that cannot be gamed or abused by branded companies.
- Maintains, at a minimum, the flexibility allowed under current FDA Guidances for ANDA sponsors to “bundle” different variations (including but not limited to dosage strengths and concentrations, container sizes, and alternative physical forms of the active ingredient (polymorphs, waters of hydration, solvates, amorphous forms) of generic products within a single ANDA.

A guidance embodying the concepts found in the Agency’s “Guidance for Industry: Variations in Drug Products that May be Included in a Single ANDA” (Dec. 1998), would accomplish

Congress' goals. The Agency is therefore urged to propound a guidance consistent with its existing policies and practices so that the drug industry can go forward with the certainty necessary to make informed business decision. When issue, the guidance should be published in draft form, and interested parties should be given at least 60 days to comment publicly to the proposal before any final Guidance is issued.

**(2) A “Substantive Determination”**

The new approval provisions of the MMA (§ 355(j)(5)(B)(iii)) provide that approval can be made effective if the court “decides that the patent is invalid or not infringed (including an substantive determination that there is no cause of action for patent infringement or invalidity) . . . .” 21 U.S.C. §§ 355(j)(5)(B)(iii)(I), (II)(aa)(AA), (III) (incorporating subclause (I); (IV) (incorporating subclause (II)). By its deliberate use of the phrase “substantive determination,” Congress spoke directly to the issue of what type of court decision will entitle an ANDA applicant to effective approval, making clear that not any decision will suffice. Despite the unambiguous nature of the statutory language, there likely are those in the industry that would benefit by a related agency regulation. The following is suggested language for a new provision, 21 C.F.R. § 314.107(b)(5):

(5) A substantive determination. A “substantive determination that there is no cause of action for patent infringement, invalidity, or unenforceability,” as used in paragraph (b)(3), refers to a court decision which precludes the patentee, NDA holder, and/or any successor in interest from bringing an infringement action on the patent against the applicant.

This provision, like the related statutory changes, would apply to any application filed after December 8, 2003 for a listed drug for which no paragraph IV certification was made before December 8, 2003. *See* MMA § 1101(c)(1).

**(3) Ensuring a Single 30-Month Stay**

Under the MMA, a patentee can obtain a 30-month stay only as to patents the information for which “was submitted to the [FDA] under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application).” 21 U.S.C. § 355(j)(5)(B)(iii) (introductory sentence). Because the statute uses the phrase “submitted” to the Agency, rather than “published” by the Agency, multiple stays are possible if the Agency does not timely list all of the patent information submitted by the NDA holder. In order to ensure that that ANDA applicants are subject to only one stay, as Congress expressly intended, NDA holders be required to confirm the accuracy of the patent listing information in the Orange Book. The NDA holder would be required to review the listed patent information and report any errors or omissions to the Agency within 10 days. The Agency would promptly

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make the necessary changes, ensuring that ANDA applicants have up to date information when preparing and submitting their applications. This new provision can be included in 21 C.F.R. § 314.53 as paragraph (g). Proposed language would include:

(g) Verification of patent information. Upon approval of the application, the application holder must verify the accuracy of the patent information published by FDA. The application holder must notify FDA within 10 days of the date that the application approval is first published of any errors or omissions in the patent information. For patent information submitted after approval of the application, the application holder must verify that the information is included in the next published supplement to the list. FDA will promptly make all changes of which it is notified. Any patent information about which the applicant fails to notify FDA within 10 days shall, once published, be considered late submission of patent information under § 314.94(a)(12)(vi).

This change applies to any patent information submitted to the Agency on or after August 18, 2003. See MMA § 1101(c)(3).