



RE: Docket No. FDA-2008-N-0483

Dear ANDA Applicant:

This letter addresses 180-day exclusivity for abbreviated new drug applications (ANDAs) referencing Merck & Co., Inc.'s COSOPT (dorzolamide hydrochloride, 2%; timolol maleate, 0.5%) ophthalmic solution (dorzolamide/timolol). Exclusivity for these products is governed by the exclusivity and forfeiture provisions in section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA or Act).¹ The statutory provisions at issue were enacted as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the MMA), Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003). FDA has not yet promulgated regulations implementing these new statutory provisions; until it does so, it will regulate directly from the statute in determining whether ANDA applicants are entitled to exclusivity.

The MMA established a new set of forfeiture events under which an applicant previously eligible for 180-day exclusivity could lose that eligibility. These provisions are quite complex and, because of the potential value of 180-day exclusivity, are of substantial interest to the regulated industry. In recognition of this interest, and to obtain the benefit of comment from interested parties on the interpretation and application of the new provisions in specific factual settings, we are establishing public dockets to receive comments on certain complex MMA forfeiture matters.² We established a docket on September 4, 2008, to permit public comments on 180-day exclusivity for dorzolamide/timolol (Docket No. FDA 2008-N-0483).

In making our decision, we have considered, among other things, a July 11, 2008 Memorandum submitted to FDA's Office of the Chief Counsel by counsel for Hi-Tech Pharmacal Co., Inc. (Hi-Tech); the July 28, 2008, and August 27, 2008 letters from Bernice Tao, Director of Regulatory Affairs at Apotex, Inc. (Apotex) to Gary Buehler, Director, Office of Generic Drugs;

¹ As we have previously stated, it is FDA's practice to make decisions on eligibility for 180-day exclusivity in the context of specific ANDAs that are otherwise eligible for approval. This approach is necessary because of the many factors that may influence eligibility for exclusivity up to the time an application is ready for approval (e.g., patent expiration, patent delisting, failure to obtain a tentative approval within 30 months, withdrawal of ANDA) and could thus render a premature eligibility determination incorrect. When the agency makes an approval decision with respect to an ANDA, it will inform an applicant affected by exclusivity that, for example, it is (1) a first applicant and entitled to exclusivity, (2) a first applicant that has forfeited its exclusivity, (3) eligible only for a tentative approval because one or more first applicants are eligible for 180-day exclusivity, or (4) eligible for approval because a first applicant has forfeited its exclusivity. Today, FDA is approving ANDAs held by Hi-Tech and Apotex for dorzolamide/timolol; therefore, we are explaining our conclusions regarding 180-day exclusivity for dorzolamide/timolol ANDAs.

² Thus far we have issued two decisions interpreting the 180-day exclusivity forfeiture provisions of the MMA using this process. See "Acarbose Decision" of May 7, 2008, in FDA Docket No. 2007-N-0445; "Granisetron Decision" of January 17, 2008, in Docket No. 2007-N-0389. We also used this process to render a decision that implicated both MMA and pre-MMA 180-day exclusivity provisions. See "Ramapril Decision" of January 29, 2008, in Docket No. 2007N-0382. These decisions are incorporated by reference here to the extent they describe interpretations of statutory provisions at issue in this matter.

submissions to Docket No. FDA 2008-N-0483; an October 17, 2008 Memorandum submitted to FDA's Office of the Chief Counsel by counsel for Hi-Tech; an October 22, 2008 Memorandum submitted to FDA's Office of the Chief Counsel by counsel for Apotex; and arguments made by Hi-Tech, Apotex, and Teva Pharmaceuticals USA, Inc., in *Hi-Tech Pharmacal, Co., Inc. v. FDA*, No. 1:08-cv-01495 (JDB).

After considering the relevant facts and applicable law, we have concluded that Hi-Tech was eligible for 180-day exclusivity for dorzolamide/timolol as a first applicant, but for the reasons described below has forfeited that eligibility. Because no applicant is eligible for 180-day exclusivity, FDA may approve any ANDA for dorzolamide/timolol that is otherwise eligible for approval.

I. Factual Background

A. Merck's New Drug Application (NDA) for COSOPT

COSOPT ophthalmic solution was approved by FDA on April 7, 1998, in NDA 20-869. Merck submitted U.S. Patent Nos. 4,797,413 (the '413 patent); 6,248,735 (the '735 patent); and 6,316,443 (the '443 patent) to FDA for listing in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for COSOPT. The '413 patent expired on April 28, 2008, with associated pediatric exclusivity expiring on October 28, 2008. The '735 and '443 patents expire on April 17, 2011. On April 18, 2006, Merck disclaimed the '735 and '443 patents. Merck submitted a request to FDA on April 26, 2006, to delist the '735 and '443 patents from the Orange Book. Merck reiterated its request by letter of December 18, 2006. On April 18, 2008, FDA published in the Orange Book the fact that Merck had requested the '735 and '443 patents be delisted. In light of this decision that Hi-Tech has forfeited exclusivity based on that patent information, we are removing the patent information from the Orange Book.

B. Abbreviated New Drug Applications (ANDAs) for Dorzolamide/timolol

There are two classes of ANDAs for dorzolamide/timolol at issue in this matter: ANDAs held by first applicants, and ANDAs held by subsequent applicants (i.e., applicants who are not first applicants). Hi-Tech's ANDA 77-847 falls into the first category; all other ANDAs for dorzolamide/timolol fall into the latter category.

Hi-Tech's ANDA was initially stamped as received by the FDA document room on August 12, 2005. FDA reviewed the application to determine whether it was sufficiently complete to permit a substantive review, as described under 21 CFR 314.101(b). On October 6, 2005, FDA refused to receive Hi-Tech's ANDA for the reasons enumerated in a letter to the company. On October 11, 2005, FDA received Hi-Tech's response to the refusal to receive letter, and the ANDA was found acceptable for filing, with a receipt date of October 11, 2005. The Hi-Tech ANDA contained paragraph IV certifications to the '413, '735, and '443 patents when submitted and received. Hi-Tech provided notice of its paragraph IV certifications to the NDA holder and patent owner, as required. Hi-Tech was sued for infringement of the '413 patent; the district court found that Hi-Tech infringed the patent and upheld its validity. *Merck & Co. Inc. v. Hi-Tech Pharmacal Co. Inc.*, No. 06-266 & 06-268, 2006 U.S. Dist. LEXIS 95820 (D.N.J. Apr. 25, 2006), *aff'd*, 482 F.3d 1317 (Fed. Cir. 2007). Hi-Tech amended its patent certification to the '413 patent from a paragraph IV certification to a paragraph III certification on April 9, 2008.

No patent infringement action regarding the '735 or '443 patents was initiated by the NDA holder or patent owner within the 45-day period following receipt of Hi-Tech's notice of paragraph IV certification. FDA tentatively approved Hi-Tech's ANDA on April 10, 2008.

Hi-Tech's October 11, 2005 receipt date made it the first applicant to submit an ANDA referencing COSOPT that contained a paragraph IV certification to a patent listed for that drug. Apotex, the next applicant that submitted an ANDA containing paragraph IV certifications to the '413, '735, and '443 patents, submitted its application on March 29, 2006. All other ANDAs containing paragraph IV certification to these patents were submitted thereafter.

Because the first ANDA containing a paragraph IV certification to a patent listed for COSOPT was submitted after December 8, 2003, 180-day exclusivity for ANDAs referencing COSOPT is governed by section 505(j)(5)(D) of the FDCA, as amended by Title XI of the MMA. *See* section 1102(b) of the MMA.

II. 180-Day Exclusivity under the MMA

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), an NDA applicant must submit information for each patent that claims the drug or method of using the drug that is the subject of the NDA. FDA publishes this patent information in the Orange Book.

An applicant must include in its ANDA one of the following certifications with respect to each patent for the listed drug it references:

- (I) that such patent information has not been filed (a paragraph I certification),
- (II) that such patent has expired (a paragraph II certification),
- (III) of the date on which such patent will expire (a paragraph III certification), or
- (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).

Section 505(j)(2)(A)(vii).³ *See also* 21 CFR 314.94(a)(12)(i)(A). An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or not infringed. Section 505(j)(2)(B). If the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order. Section 505(j)(5)(B)(iii).

³ The Act provides only one circumstance in which an ANDA applicant need not certify to a timely listed patent: "if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection," the applicant can submit "a statement that the method of use patent does not claim such a use" (referred to as a "section viii statement"). Section 505(j)(2)(A)(viii); *see also* 21 CFR 314.94(a)(12)(iv).

The MMA exclusivity provisions, like those in the earlier Hatch-Waxman Amendments, provide the first applicant(s) to submit a paragraph IV certification challenging a patent – and thus undertake the risk of litigation – an incentive in the form of the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period. The requirements for obtaining and retaining this 180-day exclusivity period are described at sections 505(j)(5)(B)(iv) and 505(j)(5)(D) of the Act.

The 180-day exclusivity period is described in the Act in terms of a delay in approval of certain ANDAs to permit one or more "first applicants" to market their generic drugs free from competition from other generic drugs approved in ANDAs. The 180-day exclusivity provision enacted in the MMA provides that

Subject to [section 505(j)(5)(D)], if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

Section 505(j)(5)(B)(iv)(I).

A "first applicant" is an applicant that "on the first day on which a substantially complete application containing a [paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV certification]." Section 505(j)(5)(B)(iv)(II)(bb).

The MMA describes a significant new feature of 180-day exclusivity in the form of a set of conditions under which an ANDA applicant that qualifies for 180-day exclusivity as a first applicant loses – or forfeits – that eligibility. Under these provisions, if certain events occur, an applicant that qualified for 180-day exclusivity at the time its ANDA was submitted may nevertheless lose any benefit from having been a first applicant to challenge a listed patent. Section 505(j)(5)(D)(i)-(iii). If all first applicants forfeit the 180-day exclusivity period, no applicant will be eligible for 180-day exclusivity and FDA may approve subsequent applicants' ANDAs subject to the approval requirements in section 505(j)(5)(B)(iii). Section 505(j)(5)(D)(iii).

A forfeiture event with respect to an application subject to the 180-day exclusivity provisions means the occurrence of any of the events identified in section 505(j)(5)(D)(i). These forfeiture events are denominated in the statute as (I) Failure to Market, (II) Withdrawal of Application, (III) Amendment of Certification, (IV) Failure to Obtain Tentative Approval, (V) Agreement with Another Applicant, the Listed Drug Holder, or a Patent Owner, and (VI) Expiration of All Patents. Only the "failure to market" forfeiture event is at issue in this matter.⁴

The failure-to-market forfeiture event provides as follows:

⁴ Hi-Tech received tentative approval of its ANDA on April 10, 2008, which was within 30 months of October 11, 2005, the date it was received, so Hi-Tech did not forfeit exclusivity pursuant to section 505(j)(5)(D)(i)(IV).

- (I) FAILURE TO MARKET. – The first applicant fails to market the drug by the later of –
- (aa) the earlier of the date that is –
 - (AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or
 - (BB) 30 months after the date of submission of the application of the first applicant; or
 - (bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:
 - (AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.
 - (BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.
 - (CC) The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b).

Section 505(j)(5)(D)(i)(I).

III. Hi-Tech's ANDA and 180-Day Exclusivity

A. Hi-Tech was Eligible for 180-day Exclusivity

Hi-Tech's application was the first substantially complete ANDA to contain a paragraph IV certification to a listed patent for COSOPT. The Hi-Tech ANDA contained paragraph IV certifications to the '413, '735, and '443 patents. Thus, at the time it submitted its ANDA, Hi-Tech was eligible for 180-day exclusivity. Hi-Tech was the only "first applicant" as described at section 505(j)(5)(B)(iv)(II)(bb) among those applicants submitting ANDAs referencing COSOPT. Because of events subsequent to submission of its ANDA, however, Hi-Tech has forfeited its eligibility for 180-day exclusivity.

B. Hi-Tech has Forfeited 180-Day Exclusivity

We have concluded that Hi-Tech is no longer eligible for 180-day exclusivity for dorzolamide/timolol. The Act provides that the 180-day exclusivity period described in section 505(j)(5)(B)(iv) "shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." Section 505(j)(5)(D)(ii). To ascertain whether a first applicant has forfeited

eligibility for exclusivity, FDA looks at each patent for which that applicant submitted a paragraph IV certification qualifying it for exclusivity. As to each such patent, FDA determines whether the applicant has lawfully maintained its paragraph IV certification and, if it has, considers whether the applicant has forfeited exclusivity under the "failure to market" provisions at section 505(j)(5)(D)(i)(I) of the Act or other relevant forfeiture provision. In this case, Hi-Tech has forfeited its exclusivity because, as to each patent for which Hi-Tech submitted a paragraph IV certification initially qualifying it as a first applicant (i.e., the '413, '735, and '443 patents), it has either forfeited exclusivity under section 505(j)(5)(D)(i)(I) of the Act ("Failure to Market") or has failed to lawfully maintain its paragraph IV certification.

For the '413 patent, Hi-Tech has failed to lawfully maintain a paragraph IV certification because it lost its patent litigation as to that patent. Specifically, in *Merck & Co. Inc. v. Hi-Tech Pharmacal Co. Inc.*, No. 06-266 & 06-268, 2006 U.S. Dist. LEXIS 95820 (D.N.J. Apr. 25, 2006), *aff'd*, 482 F.3d 1317 (Fed. Cir. 2007), the '413 patent was found to be valid and infringed by Hi-Tech's ANDA. In light of this finding, once Hi-Tech concluded its challenge to the '413 patent, it could no longer maintain a paragraph IV certification claiming that the patent was invalid or not infringed and was required to change its certification to a paragraph III acknowledging the date the patent expires. Hi-Tech did not submit its paragraph III certification to the '413 patent until April 10, 2008; however, as of June 11, 2007, when the mandate was entered upon the denial of its request for rehearing, Hi-Tech could no longer lawfully maintain its paragraph IV certification.⁵

Because Hi-Tech could not maintain its paragraph IV certification to the '413 patent after its patent loss, the '413 patent was not one "with respect to which [Hi-Tech] submitted and lawfully maintained a certification qualifying [Hi-Tech] for the 180-day exclusivity period under subparagraph [505(j)(5)(B)(iv)]." Section 505(j)(5)(D)(i)(I)(bb).

For the remaining two patents, the '443 and '735 patents, Hi-Tech lawfully maintained its paragraph IV certification. Thus, Hi-Tech would be eligible for 180 day exclusivity as to these patents unless it has forfeited eligibility for exclusivity as to these patents under the "failure to market" or other relevant forfeiture provisions. Application of the failure-to-market forfeiture provisions requires a series of analyses based on the timing of specific events. The statute directs that a forfeiture event occurs when the first applicant fails to market the drug by the *later* of two dates. One of these dates is calculated under item (aa) by determining the *earlier* of a date that is either 75 days after the first applicant's ANDA is approved (subitem (AA)) or 30 months after the date of submission of the first applicant's ANDA (subitem (BB)).⁶ Hi-Tech's

⁵ Moreover, the '413 patent expired on April 28, 2008, which would render the appropriate certification a paragraph II ("patent has expired"). Thus, as to the '413 patent, Hi-Tech has not lawfully maintained a paragraph IV certification, as required by the definition of first applicant at section 505(j)(5)(B)(iv)(II)(bb). We note that, although Hi-Tech has not forfeited exclusivity under the "Amendment of Certification" or "Expiration of All Patents" forfeiture events in section 505(j)(5)(D), these provisions direct that changes in patent certification and expiration of patents are factors in determining whether an applicant remains eligible for 180-day exclusivity.

⁶ Section 505(j)(5)(D)(i)(I)(aa)(BB) states that the 30-month period should be calculated from the date of "the submission of the application of the first applicant." In applying the MMA 180-day exclusivity provisions, FDA considers the date an ANDA containing a paragraph IV certification is submitted to be the date the ANDA is "received" pursuant to 21 CFR 314.101(b). Both this regulation, and the definition of "first applicant" at section 505(j)(5)(B)(iv)(II)(bb) of the Act, require that the ANDA containing the paragraph IV certification be substantially complete, meaning it is sufficiently complete to permit a substantive review. When an ANDA containing a paragraph IV certification is determined, upon review, to have been substantially complete as of the day it was

ANDA is being approved on October 28, 2008; the 75-day period after approval would expire on January 11, 2009. Hi-Tech submitted a substantially complete ANDA containing a paragraph IV certification on October 11, 2005; 30 months after that date was April 11, 2008. April 11, 2008, is earlier than January 11, 2009. Therefore, April 11, 2008, controls for the analysis of item (aa).

The statute directs that we look to the *later* of the dates under items (aa) and (bb) of section 505(j)(5)(D)(i)(I). Item (bb) states that the occurrence of at least one of the enumerated events, as to a first applicant or any other applicant with respect to each of the patents as to which the first applicant submitted and lawfully maintained a certification that qualified it as a first applicant, will begin a 75-day period leading to possible forfeiture of exclusivity. These (bb) events include, very generally, when a court enters a final decision that the patent is invalid or not infringed, a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed, or the patent information for the listed drug is withdrawn by the NDA holder. To date, there has been no decision or settlement in either a patent infringement case or a declaratory judgment action involving the '735 or '443 patent finding the patents invalid or not infringed.⁷ In this case, the relevant event under section 505(j)(5)(D)(i)(I)(bb) of the Act as to the '735 and '443 patents is that the NDA holder for COSOPT requested on April 26, 2006, that the '735 and '443 patents be delisted from the Orange Book. This started the running of the 75-day period as to those patents under section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act, which begins when the patent information submitted to the agency is withdrawn by the holder of the NDA.

As described above, on April 26, 2006, FDA received a letter from Merck requesting that the '735 and '443 patents be delisted from the Orange Book. On April 18, 2008, FDA published in the Orange Book the fact that Merck had requested the '735 and '443 patents be delisted. FDA did not remove the patent information from the Orange Book until after it determined (in this decision) that no applicant was entitled to exclusivity based on that patent information. Under section 505(j)(5)(D)(i)(I)(bb) of the Act, the applicable date for calculating whether a failure-to-market forfeiture event has occurred is 75 days after the patent information is withdrawn by the NDA holder. In this case, the date that is 75 days after the NDA holder withdrew the information on the '735 and '443 patents, i.e., April 26, 2006, was July 10, 2006.

Forfeiture under section 505(j)(5)(D)(i)(I) of the Act occurs if a first applicant fails to market by the later of the dates under item (aa) or (bb). The date under (aa) is April 11, 2008; the date under (bb) as to the '735 and '443 patents is July 10, 2006. Because the later date determines the date of forfeiture of exclusivity, on April 11, 2008, Hi-Tech forfeited its eligibility for 180-day

submitted to FDA, it will be deemed to have been received as of the date it was submitted (i.e., date-stamped by the appropriate FDA mail-room). When OGD sends the applicant a refusal to receive letter describing the additional information that must be submitted to render an ANDA substantially complete, the ANDA is deemed received on the day the information necessary to find the application substantially complete was submitted.

⁷ We note that Apotex unsuccessfully sought a declaratory judgment regarding the invalidity and non-infringement of the '735 and '443 patents. This action was dismissed for lack of subject matter jurisdiction by the district court. *Merck & Co. Inc. v. Apotex*, CA 06-5789, 2007 U.S. Dist. LEXIS 84426 (D.N.J. Nov. 15, 2007), *aff'd*, *Merck & Co. v. Apotex, Inc.*, 2008 U.S. App. LEXIS 18378 (Fed. Cir. Aug. 21, 2008).

exclusivity based on its certification to the '735 and '443 patents, because it failed to market its dorzolamide/timolol product by that date.⁸

C. Hi-Tech's Arguments that it is Entitled to Exclusivity are not Persuasive

Hi-Tech makes two basic arguments to support its view that it has not forfeited exclusivity. The first is that Hi-Tech's failure to market its dorzolamide/timolol product is not its fault, and thus it is inappropriate that Hi-Tech should forfeit exclusivity. In Hi-Tech's view, FDA should apply the 30-month failure-to-market provision only when the first applicant has a legal right to market its product. The second is that FDA has mishandled Merck's patent delisting request and thus cannot use the delisting as a basis for forfeiture. We address each argument below and find neither persuasive.

1. Forfeiture under Section 505(j)(5)(D)(i)(I) does not Require the ANDA Applicant be at Fault

Hi-Tech argues that for exclusivity to be forfeited under section 505(j)(5)(D)(i)(I), the eligible first applicant must have been able to market, but have failed to do so. In this case, Hi-Tech was not able to market because Merck's pediatric exclusivity blocked final approval of the ANDA; therefore, Hi-Tech asserts, it should not forfeit exclusivity for failing to market. It is Hi-Tech's view that a similar rule should pertain in applying section 505(j)(5)(D)(i)(I) any time a first applicant is unable to market its product because final approval is blocked by an unexpired patent or period of exclusivity. Hi-Tech's position is not supported by the plain language of the statute.

The use of the term "failure" in the forfeiture of exclusivity provision under section 505(j)(5)(D)(i)(I) does not require that the first applicant be at fault for failing to market its generic drug. The MMA forfeiture provisions use the term "failure" in two places, in the "failure to obtain tentative approval" and "failure to market" provisions. These provisions have notable differences in their language and structure. In the failure to obtain tentative approval provision, Congress established an express condition under which a first applicant's "failure" will not result in forfeiture. By contrast, in the failure-to-market provision, Congress has identified no circumstances that would excuse such "failure."

The "failure to obtain tentative approval" forfeiture provision identifies an express condition under which a first applicant's "failure" to obtain a tentative approval within the set timeframe will not result in forfeiture. The provision states that a forfeiture event occurs when

[t]he first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, *unless*

⁸ Even if FDA were to calculate the forfeiture event under section 505(j)(5)(D)(i)(I)(bb) of the Act from the date the request for delisting of the '735 and '443 patent information was published (which we do not believe is supported by the statutory language), Hi-Tech would have forfeited its exclusivity. Using the April 18, 2008 publication date as the date the patent was withdrawn would result in a date under (bb) of July 2, 2008. This date is the later date as between the dates in items (aa) and (bb). Hi-Tech did not market its dorzolamide/timolol product by July 2, 2008; therefore, even under this analysis, it has forfeited 180-day exclusivity.

the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

Section 505(j)(5)(D)(i)(IV) (emphasis added).⁹ In this provision Congress identified a specific situation in which a first applicant will not forfeit exclusivity; that is, a first applicant will not forfeit when certain conditions provide that it is not the applicant's fault that it could not obtain tentative approval within 30 months (i.e., that failure to obtain a tentative approval is caused by a change in or review of the requirements for approval). This express description of the circumstances in which exclusivity will not be forfeited for failure to obtain tentative approval makes it clear that, under other circumstances in which an applicant has failed to obtain tentative approval, regardless of what party might be responsible for that failure, the first applicant will forfeit exclusivity.

In contrast to the failure to obtain tentative approval forfeiture provision described above, the "failure to market" forfeiture provision contains no qualifying language that would stay or toll the forfeiture period based on events outside of the applicant's control. A failure-to-market forfeiture occurs when "the first applicant fails to market the drug by [a certain date]." Section 505(j)(5)(D)(i)(I). In the absence of any qualifying language - such as that in section 505(j)(5)(D)(i)(IV) - this forfeiture provision must be read as establishing a "no-fault" forfeiture when an applicant fails to market by one of the identified dates.

Hi-Tech's argument that it should not forfeit exclusivity for failure to market when final approval of its ANDA is blocked by a patent or exclusivity is also unpersuasive because the 180-day exclusivity provisions contain language demonstrating that Congress knew how to address the exact circumstances Hi-Tech describes and did not do so in the failure-to-market forfeiture provision. Section 505(j)(5)(B)(iv)(II)(dd) of the Act provides that when final approval is blocked by a patent or exclusivity, but the ANDA is otherwise ready for approval, the ANDA may be given a "tentative approval." By asserting that forfeiture should occur only if an ANDA applicant has obtained full approval and does not market its drug, Hi-Tech is in essence arguing that an applicant should be insulated from forfeiture if it has obtained a tentative approval in a timely fashion and the failure to market is not its fault, but rather is due to an existing patent or exclusivity. This argument is, at bottom, an argument that Congress should have conditioned forfeiture under section 505(j)(5)(D)(i)(I) on failure to obtain tentative approval, rather than on failure to market. Congress, however, knew how to create an exception for events beyond the ANDA applicant's control and chose not to do so in the failure-to-market provision. In accordance with the specific language in the statute, we apply the forfeiture under section 505(j)(5)(D)(i)(I) when an applicant fails to market, even when that failure to market is not the fault of the applicant but instead is a result of some outside factor (i.e., patent or exclusivity) over which the first applicant may have no control.¹⁰

⁹ Congress has recently clarified this provision in the FDA Amendments Act, Pub. L. 110-85, 121 Stat. 823 (Sept. 27, 2007) (FDAAA), in which it provided that, for an applicant eligible for 180-day exclusivity, if "approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates)" Section 505(q)(1)(G).

¹⁰ We note that there are any number of situations in which a first applicant might not be able to go to market because a patent or exclusivity bars final approval of its ANDA, and in which it would not want its exclusivity to be

Hi-Tech argues that the statute should be rewritten to provide an exception to the 30-month failure-to-market provision when the first applicant does not have the legal right to market on the ground that a failure to market in that circumstance is not the first applicant's fault. Even if FDA were to read a fault-based standard into the statute, however, Hi-Tech does not necessarily meet the "no fault" criteria. Hi-Tech could be considered to be at fault for having lost its patent litigation for the '413 patent. If Hi-Tech had prevailed in that litigation, approval of its ANDA would not have been delayed until the patent (and associated pediatric exclusivity) expired. Hi-Tech, however, failed in its challenge to the '413 patent, creating a bottleneck to its approval until October 28, 2008. Although Hi-Tech would potentially have been subject to additional failure-to-market trigger provisions in section 505(j)(5)(D)(i)(I)(bb) if it had prevailed in its litigation on the '413 patent, in such a scenario it is much more likely that Hi-Tech would not have been subject to forfeiture. The exception advocated by Hi-Tech simply is not in the statute, as written, and Hi-Tech's fault-based rationale for that exception does not support its argument that such an exception should apply.

Hi-Tech also argues that the MMA must be construed as requiring either actual marketing or tentative approval within 30 months, but not both, stating that it would be absurd for an applicant to obtain tentative approval within 30 months and thereby avoid forfeiture under section 505(j)(5)(D)(i)(IV), but be subject to forfeiture under section 505(j)(5)(D)(i)(I)(aa)(BB). The 30-month failure-to-market provision, however, serves a different purpose than the failure to obtain tentative approval provision, and the failure to market will only result in forfeiture if it is the later of the possible events described in section 505(j)(5)(D)(i)(I). If there is no later event under the analysis of section 505(j)(5)(D)(i)(I)(aa) and (bb) at the time that the agency makes its exclusivity determination, i.e., there is no decision or settlement of a patent litigation and no request for delisting, then there would be no forfeiture at all for failure to market within 30 months. See *Granisetron Decision* at 5. The fact that Hi-Tech forfeited exclusivity under the 30-month failure-to-market provision is a function of the timing and interplay of other events that are relevant only for the failure-to-market provisions in section 505(j)(5)(D)(i)(I), which are entirely separate from the stand-alone failure-to-obtain tentative approval provision in section 505(j)(5)(D)(i)(IV). Here, when Merck withdrew the patent information, Congress considered that event relevant vis-à-vis the 30-month failure-to-market provision in section 505(j)(5)(D)(i)(I)(aa)(BB), but not at all relevant vis-à-vis the 30-month failure-to-obtain tentative approval provision in section 505(j)(5)(D)(i)(IV). FDA's decision in this case properly implements the forfeiture provisions within the unique context of the failure-to-market provisions under section 505(j)(5)(D)(i)(I).

Finally, Hi-Tech has argued that, because it is Merck's pediatric exclusivity under section 505A of the Act that is a barrier to approval of the Hi-Tech's ANDA, FDA should rely on section 505A(m) of the Act to toll any forfeiture during the pediatric exclusivity period. The cited provision at 505A(m) was enacted in 2002, as part of the Best Pharmaceuticals for Children Act, and reauthorized by Congress in 2007 in FDAAA. It provides that

forfeited. Although in this case the pediatric exclusivity is only a six-month bar to approval, Hi-Tech's argument could apply to prevent forfeiture of exclusivity when the barrier to approval is a patent that does not expire for many years and which a first applicant either did not challenge or was unsuccessful in challenging.

If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from—

(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.

This provision at 505A(m) is not applicable to 180-day exclusivity under the MMA because by its express terms it applies only when the 180-day exclusivity period “overlaps” with a six-month pediatric exclusivity period, such that an ANDA applicant whose exclusivity has been triggered is barred from approval by the pediatric exclusivity and cannot use some or all of its 180-day exclusivity period. This may only occur under the pre-MMA provisions when the 180-day exclusivity is triggered by a court decision¹¹ and begins to run, but the ANDA applicant is unable to market its product because of 6-month pediatric exclusivity attached to another patent that - but for the associated pediatric exclusivity - would no longer be a barrier to approval of the ANDA. In that case, the ANDA applicant is entitled to have the number of days of 180-day exclusivity it loses because it cannot market its drug due to the pediatric exclusivity added to the period during which it can market after the pediatric exclusivity expires.

The present case arises under the MMA 180-day exclusivity provisions, and thus section 505A(m) does not apply. Under the current statutory provisions, unlike under the pre-MMA provisions, 180-day exclusivity can be triggered only by commercial marketing. The MMA provisions do not contain a “court decision” trigger that could begin the 180-day exclusivity period before the ANDA applicant is able to market and thus could result in overlapping 180-day exclusivity and pediatric exclusivity. Under the MMA provisions, the 180-day period can begin only on the date of first commercial marketing of the drug by a first applicant, and an ANDA applicant will not be able to obtain final approval and market until any applicable pediatric

¹¹ The pre-MMA 180-day exclusivity provision at 505(j)(5)(B)(iv) reads:

If the application contains a certification described in subclause IV of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-

(I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application, or
(II) the date of a decision of a court in action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

exclusivity has expired. Section 505(j)(5)(B)(iv)(I). Thus, the situation where 180-day exclusivity is triggered and running but the ANDA applicant is prevented from obtaining approval and marketing will not arise. Hi-Tech's situation therefore does not - and cannot - involve the tolling of the running of 180-day exclusivity when there is overlap between that exclusivity and pediatric exclusivity. Instead, Hi-Tech is arguing that 180-day exclusivity - although it has not begun and thus cannot overlap Merck's pediatric exclusivity - should not be forfeited during the pediatric exclusivity period. Section 505A(m) as written requires an overlap between 180-day marketing exclusivity and pediatric exclusivity, and cannot apply when there is no such overlap under the MMA. Given that section 505A(m) has been reauthorized since passage of the MMA, Congress could have revised the provision to address 180-day exclusivity under the MMA as well as exclusivity under the pre-MMA provision. Congress has not, however, done so. Nor is the requirement of an "overlap" irrelevant following passage of the MMA, because the pre-MMA exclusivity statute still applies for drugs for which the first ANDA containing a paragraph IV certification was filed before the effective date of the MMA. Therefore, there is no statutory basis on which to toll the failure-to-market forfeiture event because of the innovator's pediatric exclusivity.

2. Merck's Patent Withdrawal Request Resulted in Forfeiture

One of the failure-to-market forfeiture events can occur if "the patent information submitted under [section 505(b) or (c)] is withdrawn by the holder of the [reference listed drug]." Section 505(j)(5)(D)(i)(I)(bb)(CC). Hi-Tech asserts that FDA has mishandled Merck's request that the '735 and '443 patents be delisted and thus the withdrawal of the patents cannot be the basis for forfeiture of Hi-Tech's exclusivity. We do not agree. The delisting by Merck of the '735 and '443 patents is appropriately a factor in calculating whether a forfeiture of Hi-Tech's exclusivity has occurred.

As described above, the 180-day exclusivity provision at section 505(j)(5)(B)(iv) directs that, if a subsequent ANDA contains a paragraph IV certification and is for the same drug for which a first applicant has submitted an ANDA containing a paragraph IV certification, the subsequent applicant's ANDA can be approved 180 days after the first applicant begins commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant. Thus, as a threshold matter, for the 180-day exclusivity provision to apply at all, first and subsequent applicants must have paragraph IV certifications to a given patent.

FDA has implemented the patent withdrawal provision so as to preserve 180-day exclusivity for first applicants by retaining that patent information in the Orange Book until the agency has determined that the first applicants with certifications to those patents have either used or forfeited the exclusivity period. If FDA were to immediately remove the patent information from the Orange Book upon the request by the NDA holder that the patent be withdrawn, no ANDA applicant could maintain a paragraph IV certification to the patent, the threshold requirement for 180-day exclusivity (i.e., first and subsequent applicant's paragraph IV certifications) would no longer exist and, under the plain language of section 505(j)(5)(B)(iv)(I), FDA would not delay the approval of any subsequent application. This immediate loss of eligibility for exclusivity would be inconsistent with the express language of section 505(j)(5)(D)(i)(I)(bb)(CC), which contemplates that for at least 75 days after the patent is withdrawn by the NDA holder, a first applicant will maintain its eligibility to begin its 180-day

exclusivity period. Thus, although FDA considers the patents to be withdrawn on the date that FDA receives the NDA holder's delisting request for purposes of forfeiture, FDA will not actually delist those patents until it has determined that delisting would not deprive a first applicant of an exclusivity period, if that exclusivity period has not been forfeited.

In the present case, FDA maintained the listing of the '735 and '443 patents to preserve Hi-Tech's potential exclusivity until it determined that Hi-Tech had forfeited exclusivity. That continued listing cannot vest Hi-Tech with exclusivity as if Merck had never withdrawn its patent information. FDA must give proper effect to both the exclusivity and forfeiture provisions in the MMA, as it has done here.¹² The agency identifies a patent the sponsor has requested be withdrawn with a notation that delisting has been requested. The listing for the '735 and '443 patents in the Orange Book is accompanied by the notation "delist requested."¹³ When a patent is so identified in the Orange Book, pending ANDA applicants will maintain their current certification to the patent, and any new ANDA applicant must submit either a paragraph III or paragraph IV certification to the patent. These certifications are necessary to ensure that a first applicant's exclusivity is not undermined by the absence of certifications to the patent in subsequent ANDAs. FDA will leave information related to withdrawn patents in the Orange Book and thus maintain the need for corresponding certifications in pending ANDAs until it has determined that any related 180-day exclusivity has expired or been forfeited. In this case, the information for the '735 and '443 patents has been retained in the Orange Book until the agency determined at the time of approval that Hi-Tech had forfeited exclusivity.

Hi-Tech has raised a number of objections to FDA's handling of the patent delisting request. It asserts that FDA cannot both treat the patent as withdrawn for forfeiture purposes and maintain the patent information in the Orange Book; that the rule of *Ranbaxy Labs., Ltd. v. Leavitt*, 469 F.3d 120 (D.C. Cir. 2006), applies to prevent FDA from delisting the patent until the first applicant's exclusivity has expired; that the patents could not have been withdrawn because Apotex brought a declaratory judgment suit for those patents; and that FDA's failure to publish the delisting request for the '735 and '443 patents until April of 2008 bars forfeiture based on the NDA holder's delisting request. None of these arguments is persuasive.

As an initial matter, FDA's continued listing of the patent information pertaining to the '735 and '443 patents in the Orange Book is an appropriate and reasonable way to implement the statute. As described above, continued listing of the information is a means to protect the first applicant's potential exclusivity. As the court found in *Ranbaxy*, to protect an applicant's eligibility for exclusivity, it is appropriate for the agency to retain in the Orange Book information on patents the sponsors have requested be delisted. 469 F.3d at 126.

¹² Section 505(j)(5)(D)(i)(I)(bb)(CC) refers to "patent information" being "withdrawn," indicating that withdrawal of the patents is an action taken by the NDA holder independently of whether and when FDA publishes the withdrawal as a delisting in the Orange Book. Congress's use of "withdrawn" rather than "delist" (which is how FDA generally refers to removing patent information from the Orange Book upon the NDA holder's request) supports FDA's approach to maintain its listing independently of the withdrawal, so as to properly maintain potential exclusivity and give effect to forfeiture events.

¹³ See Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020869&Product_No=001&table1=OB_Rx.

We also have considered and rejected in both this case and in the matter described in the Acarbose Decision, the argument that eligibility for 180-day exclusivity following the NDA holder's voluntary withdrawal of its patent should be governed not by the MMA forfeiture provisions, but by the rule established in *Ranbaxy*. *Ranbaxy* held that FDA may not condition the delisting of a patent on the existence of patent litigation, and thus deprive an ANDA applicant that had submitted the first ANDA to contain a paragraph IV certification of a period of marketing exclusivity for which it would otherwise be eligible. 469 F.3d at 125-26. That holding does not apply to the MMA, which expressly provides that patent withdrawal may serve as a basis to forfeit exclusivity. The *Ranbaxy* court noted that the decisions rendered by the FDA and the district court had been made pursuant to the Act "as it stood before the MMA and, because the MMA was not made retroactive ... this decision is also geared to the Act pre-MMA." 469 F.3d at 122.¹⁴ Therefore, the court did not purport to render a decision on patent delisting and exclusivity under the MMA.¹⁵

Nor does the patent withdrawal forfeiture provision confer undue power on an NDA holder to inappropriately divest a first applicant of its eligibility for exclusivity by withdrawing patent information.¹⁶ An NDA holder's delisting request will not cause forfeiture unless the first applicant's exclusivity is based only upon those patents that have been withdrawn, and only when forfeiture is otherwise applicable under the approach described in section 505(j)(5)(D)(i)(I). Moreover, forfeiture may occur only after the ANDA applicant has been given 75 days within which to begin marketing (after which it would enjoy the entire benefit of the 180-day exclusivity period). Section 505(j)(5)(D)(i)(I)(bb). In addition, it seems unlikely that NDA holders would engage in a concerted practice to divest first applicants of exclusivity by delisting patents, because NDA holders lose less market share if there is a 180-day exclusivity period in which they share the market only with the first applicant, as opposed to facing competition from all approvable ANDA applicants. See "Generic Competition and Drug Prices," available at http://www.fda.gov/cder/ogd/generic_competition.htm.

Moreover, that the continued listing of the '735 and '443 patents gave rise to a paragraph IV patent challenge by Apotex and a related attempt to obtain a declaratory judgment pertaining to

¹⁴ Congress passed the MMA on December 8, 2003, well before the D.C. Circuit affirmed the district court in *Ranbaxy* on November 14, 2006. As a matter of timing, Congress could not have even been aware of the *Ranbaxy* holding.

¹⁵ In addition, as noted in the Acarbose Decision at pp. 8-9, we also have considered the argument that the forfeiture event described in section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act applies only if the withdrawal of a patent is pursuant to the process described at section 505(j)(5)(C)(ii) of the Act. Section 505(j)(5)(C)(ii) contemplates that, as a result of a counterclaim by the ANDA applicant in patent infringement litigation, a court may issue an order requiring that patent information be corrected or deleted. Only in that situation, the argument goes, would the withdrawal of patent information trigger the statutory forfeiture provision. The effect of patent delisting on eligibility for 180-day exclusivity is expressly addressed by the plain language of section 505(j)(5)(D)(i)(I) of the Act. We agree that, if a patent were withdrawn by the NDA holder as a result of a counterclaim by an ANDA applicant, a first applicant's continued eligibility for 180-day exclusivity would be governed by section 505(j)(5)(D)(i)(I); however, the scope of the patent delisting forfeiture provision is much broader. Section 505(j)(5)(D)(i)(I)(bb)(CC) applies to more than just those patents withdrawn as a result of a counterclaim; on its face, it applies when "[t]he patent information ... is withdrawn by the holder of the [NDA]." FDA reads the plain language of 505(j)(5)(D)(i)(I)(bb)(CC) to apply whenever a patent is withdrawn (or requested to be "delisted") by the NDA holder.

¹⁶ NDA holders already have significant power under the statutory scheme to list patents and thereby create the possibility that a first applicant may benefit from 180-day exclusivity (and that competition from multiple lower-priced generic products will be delayed accordingly).

those patents has no effect on the forfeiture of exclusivity related to the patent withdrawal. In both this case and the case described in the Acarbose Decision, applicants have attempted to obtain declaratory judgments on patent validity or infringement after the PTO had published disclaimers pertaining to the patent. In this case, on April 18, 2006, Merck disclaimed all the claims of the '735 and '443 patents (and requested that those patents be delisted from the Orange Book on April 26, 2006) before Apotex unsuccessfully sought a declaratory judgment regarding the invalidity and non-infringement of the patents. *Merck & Co. Inc. v. Apotex*, CA 06-5789, 2007 U.S. Dist. LEXIS 84426 (D.N.J. Nov. 15, 2007), *aff'd*, *Merck & Co. v. Apotex, Inc.*, 2008 U.S. App. LEXIS 18378 (Fed. Cir. Aug. 21, 2008); *see also* Acarbose Decision at p.2 n.3 (Cobalt initiated its declaratory judgment action well after the PTO had published the disclaimer of all the claims of the patent and then voluntarily dismissed case). Hi-Tech asserts that FDA cannot “oust the courts from jurisdiction after the fact” by deciding now that the patents are delisted. See July 11, 2008 Letter at 9. However, FDA’s approach in this case does not undermine any court action, and appropriately preserved potential exclusivity for Hi-Tech until FDA determined that there could be no exclusivity based on the patents that Merck had withdrawn. Regardless, the Federal Circuit in fact affirmed the district court’s dismissal of the case for lack of subject matter jurisdiction, and never addressed whether jurisdiction might be additionally lacking because of the delisting request. *Merck & Co. v. Apotex, Inc.*, 2008 U.S. App. LEXIS 18378 (Fed. Cir. Aug. 21, 2008). That court’s decision that there was no “case or controversy” relating to Apotex’s counterclaim for a declaration of noninfringement and/or invalidity simply has no bearing on FDA’s implementation of the clear language of the forfeiture provisions in the FDCA.

Finally, Hi-Tech has argued that because FDA did not publish the fact that patent delisting had been requested until April 18, 2008, the withdrawal by Merck of the '735 and '443 patents could not serve as a basis for forfeiture. We do not agree. First, as noted above at n. 8, even if FDA were to calculate the forfeiture event using the April 18, 2008 publication date as the date the patent was withdrawn, Hi-Tech would have forfeited its exclusivity because it did not market its dorzolamide/timolol product by July 2, 2008. This is not a case in which, had FDA published the patent delisting earlier, Hi-Tech could have taken steps to speed the approval of its application. As of April 26, 2006, when Merck first submitted its patent delisting request, the district court hearing the patent infringement case involving the '413 patent had already determined that the '413 patent was valid and entered judgment against Hi-Tech. *Merck & Co. Inc. v. Hi-Tech Pharmacal Co. Inc.*, No. 06-266 & 06-268, 2006 U.S. Dist. LEXIS 95820 (D.N.J. Apr. 25, 2006). This decision was affirmed by the Federal Circuit. 482 F.3d 1317 (Fed. Cir. 2007). The finding that the '413 patent was valid created a barrier to approval of the Hi-Tech patent that earlier notice of the patent delisting request could not have overcome.¹⁷ Moreover, Hi-Tech was clearly on notice of Merck’s request to delist the patents, even before FDA published that request for delisting, as that request was publicly noted in the court’s decision in the declaratory judgment action brought by Apotex. *Merck & Co. Inc. v. Apotex*, CA 06-5789, 2007 U.S. Dist. LEXIS 84426 (D.N.J. Nov. 15, 2007).

¹⁷ Although the delay in publishing information regarding Merck’s patent delisting request did not affect the outcome in this case, it was nonetheless unfortunate that the agency did not publish this information sooner. Under the agency’s current practice, when a sponsor requests delisting of a patent, FDA publishes the fact of that request promptly after receipt.

IV. Conclusion

After consideration of the Hi-Tech ANDA, the applicable law, and the comments submitted by interested parties, we have concluded that Hi-Tech was eligible for 180-day exclusivity for the '735 and '443 patents, but that exclusivity was forfeited under the failure-to-market provisions at section 505(j)(5)(D)(i)(I) of the Act. Because Hi-Tech has forfeited 180-day exclusivity, FDA may approve any ANDA for dorzolamide/timolol that is otherwise eligible for approval.

Sincerely,

{See appended electronic signature}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Gary Buehler
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