



William A. Rakoczy, Esq.
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 West Hubbard St.
Suite 500
Chicago, IL 60610

Dear Mr. Rakoczy:

This letter addresses the eligibility of Cobalt Pharmaceuticals, Inc. (Cobalt) for 180-day exclusivity for acarbose tablets, for which it has submitted abbreviated new drug application (ANDA) No. 77-532. We are responding to issues raised in submissions to the Food and Drug Administration (FDA) from Cobalt and others (see attached listing) regarding the applicability to this ANDA of 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).

After considering the facts and applicable law, we have concluded that Cobalt was eligible for 180-day exclusivity for acarbose tablets as a first applicant, but for the reason described below, has forfeited that eligibility. Because no applicant is eligible for 180-day exclusivity, FDA may approve any ANDA for acarbose tablets that is otherwise eligible for approval.

I. Factual Background

A. Bayer's New Drug Application for Precose

Precose 25-mg and 50-mg tablets were approved on September 6, 1995. The 100-mg strength of Precose tablets was approved on May 29, 1997. Bayer submitted U.S. Patent No. 4,904,769 (the '769 patent) to FDA for listing in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for all strengths of Precose tablets. On April 16, 2007, Bayer requested that the '769 patent be delisted from the Orange Book.² On September 25, 2007, FDA published the request for delisting in the Orange Book.

¹ You have requested that FDA explain Cobalt's eligibility for 180-day exclusivity and the application of the forfeiture provisions to its ANDA. 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 Cobalt and by Roxane Laboratories, Inc. (Roxane) for acarbose tablets; therefore, we are explaining our conclusions regarding 180-day exclusivity for these products.

² By letter dated April 11, 2007, to FDA's Drug Information Service Branch, Cobalt raised questions regarding the patent information that was published in the Orange Book for Precose. Pursuant to 21 CFR 314.53(f), Cobalt

B. Cobalt's Abbreviated New Drug Application for Acarbose Tablets

Cobalt's ANDA was initially stamped as received by the FDA document room on January 14, 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 March 9, 2005, FDA refused to receive Cobalt's ANDA for several reasons, which were enumerated in a letter to the company. On March 22, 2005, FDA received Cobalt's response to the refusal to receive letter, and the ANDA was found acceptable for filing, with a receipt date of March 22, 2005. The Cobalt ANDA contained a paragraph IV certification to the '769 patent, which is the only patent at issue in this matter. Cobalt was the first applicant to submit an ANDA referencing Precose that contained a paragraph IV certification to a patent listed for that drug. Cobalt provided notice of its paragraph IV certification to the NDA holder and patent owner, as required. No patent infringement action was initiated by the NDA holder or patent owner within the 45-day period following receipt of Cobalt's notice of paragraph IV certification. On October 17, 2007, Cobalt brought a declaratory judgment action against the patent owner and NDA holder (*Cobalt Pharmaceuticals Inc. v. Bayer Aktiengesellschaft*, No. 07CV5875 (N.D. Ill. filed Oct. 17, 2007)). The court granted Cobalt's notice of voluntary dismissal, without prejudice, on February 20, 2008.³

Cobalt's ANDA contained in vivo bioequivalence studies, which had been conducted before Cobalt received FDA's bioequivalence recommendations.⁴ The bioequivalence recommendations for acarbose were sent by FDA to Cobalt on January 6, 2005, and contained information related to both in vivo and in vitro methodologies. The bioequivalence data Cobalt submitted with its ANDA were deficient. Over the course of its consideration of Cobalt's ANDA, the agency sent Cobalt a number of letters describing deficiencies in the application. Cobalt responded to these deficiencies. The last step of the application review involved

disputed the accuracy of the Precose patent information and requested that FDA require the New Drug Application (NDA) holder (Bayer) to correct the patent information to reflect the grant of a patent term extension to the '769 patent which extended the patent expiration date from February 27, 2007, to September 6, 2009. On April 12, 2007, FDA's Office of Drug Information forwarded a redacted copy of Cobalt's correspondence to Bayer and requested a prompt response. On April 16, 2007, Bayer informed FDA that the assignee of interest of the '769 patent, Bayer Healthcare AG, had filed a statutory disclaimer under 35 U.S.C. 253, disclaiming all issued claims of the '769 patent, and that the filed disclaimer had been published by the USPTO on February 27, 2007. Bayer further stated that "[i]n view of this disclaimer, the NDA-holder Bayer Pharmaceuticals Corporation hereby requests that the '769 patent be de-listed from the Orange Book."

³ We note that Cobalt initiated its declaratory judgment action regarding the '769 patent well after the PTO had published the disclaimer to all claims of the '769 patent by its assignee and on the same day that it submitted its first comment to the docket established by FDA on September 26, 2007, regarding certain legal/regulatory issues that pertain to generic drug applications for acarbose tablets.

⁴ On September 5, 2003, Cobalt had written to the Office of Generic Drugs (OGD) seeking guidance on the development of bioequivalence criteria for acarbose tablets. Acarbose is a non-systemically absorbed oligosaccharide that reversibly inhibits α -glucosidases. Its mechanism of action is not by means of systemic absorption, rather its antihyperglycemic action is by means of enzyme inhibition in the intestines. Conventional bioequivalence criteria for systemically absorbed products therefore would not apply to acarbose. Because of these factors, and due to other priorities, OGD did not provide bioequivalence guidance for acarbose until January 6, 2005. ANDA applicants are not required to await product-specific guidance from FDA before they begin their bioequivalence studies; however, the information provided in such guidance may be useful to the applicant and prevent the need for additional studies should those conducted by the applicant not be acceptable for establishing bioequivalence.

inspection of the Australian facility used by Cobalt to conduct the bioequivalence studies, which had not previously been inspected and which FDA did not plan to inspect until it had determined that the studies conducted at the facility were otherwise acceptable to support approval of the ANDA. On December 11, 2007, after conducting an off-site data audit, FDA determined that the Australian facility used by Cobalt was acceptable.⁵

On October 24, 2007, Cobalt submitted an "Emergency Petition for Stay of Action" requesting that FDA stay approval of any subsequent ANDAs for acarbose tablets until Cobalt's 180-day exclusivity expires (Docket 2007P-0414).⁶ Sixteen days later, on November 9, 2007, Cobalt submitted a Citizen Petition and another Emergency Petition for Stay of Action challenging as inadequate and inappropriate the in vitro bioequivalence recommendations FDA had provided to Cobalt in January 2005, and requesting the agency stay approvals of all ANDAs until they contain adequate in vivo bioequivalence data (Docket 2007P-0448).⁷ These November 2007 petitions appear to have been based on the assumption that other ANDA applicants had chosen to conduct in vitro bioequivalence studies, rather than in vivo bioequivalence studies such as those conducted by Cobalt.

The issues raised in Cobalt's petition triggered a reassessment of appropriate in vitro and in vitro bioequivalence methodologies for acarbose tablets. This assessment was conducted by staff from the Office of Generic Drugs and from the Office of Clinical Pharmacology with input from the Division of Metabolism and Endocrine Products. While it reviewed the question whether the methods used by Cobalt and other applicants were adequate to establish bioequivalence for acarbose, FDA delayed approval of the acarbose ANDAs. FDA determined, as required by section 505(q) of the Act, that such a delay was necessary to protect the public health. The agency has completed its review of the bioequivalence issues, and is responding to your petitions on that issue in a separate letter. Because both in vitro and in vivo methods may be appropriate for establishing bioequivalence for acarbose products, FDA may approve Cobalt's ANDA and ANDAs containing appropriate in vitro bioequivalence data.

II. Abbreviated New Drug Applications and 180-day Exclusivity

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 and for which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the

⁵ OGD requests an inspection of clinical facilities or analytical laboratories conducting BE studies included in an unapproved ANDA if there is a question about the quality or integrity of the data submitted in an ANDA; or if a clinical facility or analytical testing site is identified in the ANDA that has no inspection history, was classified "official action indicated" on its last inspection, or has not been inspected within the past 3 years; or a clinical facility and/or analytical laboratory is performing a non-conventional BE study for which it has never been inspected (e.g., a study using pharmacodynamic endpoints to assess bioequivalence). The inspection of the Australian facility was necessitated by the fact that it had no inspection history as well as the non-conventional nature of the BE study.

⁶ The docket number was changed to FDA-2007-P-0249 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

⁷ The docket number was changed to FDA-2007-P-0418 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

manufacture, use, or sale of the drug" (sections 505(b)(1) and (c)(2) of the Act). 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).⁸ 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) of the Act). 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) of the Act).

The MMA exclusivity provisions, like those in the 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.

Section 505(j)(5)(D) describes a significant new feature of 180-day exclusivity under the MMA in the form of a set of conditions under which an ANDA applicant loses — or forfeits — eligibility for 180-day exclusivity. These are the provisions at issue in this matter.

A. Cobalt's Eligibility for 180-day Exclusivity

Cobalt's ANDA 77-532 was the first ANDA that contained a paragraph IV certification to a listed patent for Precose. Because this ANDA was submitted after December 8, 2003, 180-day exclusivity for ANDAs referencing Precose 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). 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.

⁸ The Act provides only one circumstance in which an ANDA applicant need not certify to a 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 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 value of 180-day exclusivity, are of substantial interest to 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 MMA issues. Because of the complex regulatory issues related to Cobalt's eligibility for exclusivity, we solicited comments on the matter from acarbose ANDA applicants and established a public docket to receive comments from other interested persons.⁹ In considering the applicability of the MMA forfeiture and exclusivity provisions to the acarbose ANDAs, we have considered the views of Cobalt and the other parties submitting comments.

B. Forfeiture of Exclusivity

After considering the Cobalt ANDA in light of the MMA forfeiture provisions, we have determined that ANDA 77-532 for acarbose tablets is no longer eligible for 180-day exclusivity. 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) of the Act). Cobalt has forfeited its exclusivity because a forfeiture event as to the '769 patent has occurred under section 505(j)(5)(D)(i)(I) of the Act ("Failure to Market"). We also have analyzed forfeiture of Cobalt's exclusivity under section 505(j)(5)(D)(i)(IV) of the Act ("Failure to Obtain Tentative Approval"). This letter discusses the application of each provision in turn.

1. Cobalt has Forfeited Exclusivity for Failure to Market

Under section 505(j)(5)(D)(i)(I) of the Act, a forfeiture event arises whenever any of the following occurs:

- (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

⁹ Comments were initially submitted to OGD in response to OGD's correspondence # 07-1254 of September 26, 2007 (attached), which had solicited comment on legal and regulatory issues. The public docket was assigned docket number 2007N-0417. The docket number was changed to FDA-2007-N-0445 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. FDA has used a similar process to solicit comments on exclusivity issues related to granisitrone hydrochloride injection (Docket 2007N-0389) and ramipril capsules (Docket 2007N-0382).

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).

Application of these 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)).¹⁰ Cobalt's ANDA is being approved on May 7, 2008; the 75 day period would expire on July 21, 2008. Cobalt submitted a substantially complete ANDA containing a paragraph IV certification on March 22, 2005; 30 months from that was September 22, 2007. September 22, 2007 is earlier than July 21, 2008. Therefore, September 22, 2007, 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 applicant¹¹ will begin a 75-day period leading to possible

¹⁰ 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 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.

¹¹ Item (bb) looks to the occurrence of any of the enumerated events "with respect to the first applicant or any other applicant (which other applicant has received tentative approval)." This language reasonably anticipates that a first applicant will not forfeit its exclusivity unless another applicant has met the technical and scientific requirements for approval of its ANDA. There are, however, applications not eligible for tentative approval (i.e., because there are no unexpired patents, 30-month stay, or exclusivity) that may otherwise be ready for final approval. As to these applications — for which there are no barriers to marketing but the first applicant's eligibility for 180-day

forfeiture of exclusivity. These 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, no action for infringement of the '769 patent has been brought against Cobalt or any subsequent applicant. As noted in the background on Cobalt's ANDA above, on October 17, 2007, Cobalt filed an action for declaratory judgment of non-infringement and invalidity of the '769 patent. This case has been voluntarily dismissed without prejudice. No court has entered a final judgment of invalidity or non-infringement, and no court has signed a settlement order or consent decree entering final judgment of invalidity or non-infringement. Therefore, neither of the litigation-related events factor into the forfeiture analysis. In this case, the relevant event under section 505(j)(5)(D)(i)(I)(bb) of the Act is that the NDA holder for Precose requested on April 16, 2007, that the '769 patent be delisted from the Orange Book. This triggered the start of the 75-day period 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.

On April 16, 2007, FDA received a letter from Bayer Pharmaceuticals Corporation advising the Agency that all issued claims of the '796 patent had been disclaimed by the patent assignee of interest.¹² Accordingly, Bayer requested that the '796 patent be delisted from the Orange Book for the Precose NDA 20-482. The request for patent delisting was noted in the Orange Book on September 25, 2007.¹³ 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 '796 patent, i.e., April 16, 2007, was June 30, 2007.

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 September 22, 2007, date under section 505(j)(5)(D)(i)(I)(aa) is the later date, therefore it is the date that controls. Cobalt forfeited its

exclusivity — forfeiture of a first applicant's exclusivity will have the effect of permitting immediate approval and marketing of generic products. Therefore, in applying section 505(j)(5)(D)(i)(I), the agency will look both to whether there are other applicants that have received tentative approval and whether there are other applicants that have met the requirements for approval under section 505(j) and would be eligible for final approval with the forfeiture of the first applicant's exclusivity. We note, for example, that Roxane's ANDA for acarbose was not eligible for tentative approval on the basis of a 30-month stay or (upon withdrawal of the '769 patent) an unexpired patent blocking final approval.

¹² See footnote 2.

¹³ The publication of the request for patent delisting in the Orange Book was accompanied by an annotation reading "Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period." Because immediate removal of patent information from the Orange Book upon withdrawal of the patent information by the NDA holder could result in ANDA applicants withdrawing corresponding patent certifications prematurely and thus undermining a first applicant's exclusivity, FDA will leave information related to withdrawn patents in the Orange Book until it has determined that any related 180-day exclusivity has expired. In this case, the patent information was retained in the Orange Book until the agency could resolve these complex issues and respond to Cobalt's questions regarding its eligibility for 180-day exclusivity. We interpret the NDA holder's request for patent delisting to constitute withdrawal of the patent information under section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act.

180-day exclusivity on September 22, 2007, because it did not begin to market its acarbose product by that date.¹⁴

We have considered and rejected the argument made in comments to FDA's docket 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 Labs., Ltd. v. Leavitt*, 469 F.3d 120 (D.C. Cir. 2006). *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 (see 469 F.3d at 125-26). These comments argue 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.

We do not find this argument persuasive. First, 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). Therefore, the court did not purport to render a decision on patent delisting and exclusivity under the MMA. 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 with the comment 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]." Therefore, 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.

That section 505(j)(5)(D)(i)(I)(bb) of the Act is broadly applicable to all patent withdrawals is apparent from the text of the provision. Unlike subitems (AA) and (BB) of section 505(j)(5)(D)(i)(I)(bb), which begin with "[i]n an infringement action ...," and thus anticipate events occurring in the context of litigation, subitem (CC) contains no prefatory language suggesting that it applies only in the context of infringement litigation. Moreover, subitem (CC) does not refer to section 505(j)(5)(C)(ii) of the Act, i.e., the counterclaim provision, nor does section 505(j)(5)(C)(ii) refer to subitem (CC). Because subitem (CC) is not limited by its terms

¹⁴ 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 delisting of the '796 patent information was published (which we do not believe is supported by the statutory language), Cobalt would still forfeit exclusivity. If the agency were to use the September 25, 2007, publication date as the date the patent was withdrawn, the date that is 75 days later is December 9, 2007. This date under item (bb) is later than the September 22, 2007 date under item (aa); therefore the later date as between items (aa) and (bb) would be December 9, 2007. Cobalt did not market its acarbose product by December 9, 2007, so even under this analysis, it has forfeited 180-day exclusivity.

to a particular context in which the patent withdrawal occurs, it applies whenever an NDA holder withdraws a patent.

In addition to being consistent with the plain language of section 505(j)(5)(D)(i)(I) of the Act, there are a number of additional considerations that support the application of the statutory forfeiture provisions whenever a patent is withdrawn by the NDA holder. The forfeiture provisions are structured such that, even if a patent is withdrawn as a direct result of an ANDA applicant's counterclaim seeking such withdrawal, the first applicant will have only the period contemplated under the appropriate "failure to market" period of section 505(j)(5)(D)(i)(I) within which to begin commercial marketing and use its exclusivity. Given this time-limited period of eligibility for exclusivity even when the patent delisting is a direct result of an ANDA applicant's efforts, it would make little sense to provide a potentially longer period of eligibility for exclusivity (i.e., until the first applicant's exclusivity has been triggered and run or the patent expires) when the NDA holder withdraws the patent voluntarily or for reasons unrelated to an ANDA applicant's counterclaim in patent litigation (e.g., because of a decision by the patent owner or NDA holder that the patent does not claim the approved drug product or its use, or as part of an FTC settlement). Therefore, FDA sees no basis for applying the forfeiture provision of 505(j)(5)(D)(i)(I) only in cases when a patent is withdrawn pursuant to an ANDA applicant's counterclaim in a patent infringement case.

2. Cobalt has not Forfeited under the Failure to Obtain Tentative Approval Forfeiture Provision

The MMA also established that an ANDA applicant forfeits exclusivity if it fails to obtain a tentative approval within a given period of time. Under this provision, 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 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).

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) of the Act). The term "tentative approval" means notification to an applicant by FDA that an ANDA "meets the requirements of [505(j)(2)(A)], but cannot receive effective approval because there is [a patent or period of exclusivity protecting the listed drug]" (section 505(j)(5)(B)(iv)(II)(dd) of the Act).

To calculate the start of the 30-month period under this forfeiture provision, it is reasonable to use the date that qualifies the applicant as a first applicant for 180-day exclusivity purposes: the date the ANDA is sufficiently complete to permit a substantive review.¹⁵ A first applicant's

¹⁵ We note that, in contrast, the failure to market provision at section 505(j)(5)(D)(i)(I)(aa)(BB) of the Act calculates the 30-month period from the date of "submission," rather than the date the application is "filed." The exclusivity

ANDA must be a "substantially complete application" (section 505(j)(5)(B)(iv)(II)(bb)). A "substantially complete application" is an application that "on its face is sufficiently complete to permit substantive review and contains all the information required by [section 505(j)(2)(A)]" (section 505(j)(5)(B)(iv)(II)(cc)). The first applicant's submission of an ANDA that is determined to be sufficiently complete to permit review establishes eligibility for the benefits of 180-day exclusivity, and carries with it the requirement that — to maintain that eligibility — the first applicant must work diligently to obtain a tentative approval before the 30-month period expires.

Cobalt's ANDA was sufficiently complete to permit review and was received¹⁶ on March 22, 2005. Therefore, the date that would be used to calculate both whether Cobalt was a first applicant for 180-day exclusivity purposes and the date from which the 30-month forfeiture period would begin to run is March 22, 2005, as that is the date upon which the ANDA both contained a paragraph IV certification and was determined to be substantially complete. The 30-month period began on March 22, 2005, and ended on September 22, 2007. Cobalt had not received either a tentative approval or an approval as of that date.

The failure to obtain tentative approval provision requires that an applicant obtain a tentative approval within 30 months after the date on which the application is filed, unless that 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)). 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 (such as Cobalt), 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) of the Act).¹⁷ We note that no petition related to acarbose was submitted until November 9, 2007, when Cobalt itself submitted a citizen petition and petition for stay regarding the appropriate methodology for establishing bioequivalence for acarbose products.

provisions appear to use the terms "submit" and "file" interchangeably; there is no evidence that Congress intended a difference in meaning between these latter two terms. Because both terms are used in the context of "first applicant" status, we will interpret the terms to refer to the time that the agency has determined ANDA to be sufficiently complete to permit substantive review. If we interpreted the term "submission" in this context to mean the date the ANDA is date-stamped by FDA, regardless of whether the application is found to have been reviewable, an applicant whose ANDA cannot be reviewed without the submission of additional information would find its failure to market period under section 505(j)(5)(D)(i)(I)(aa)(BB) to have begun to run even before the agency could begin a substantive review of the application.

¹⁶ FDA's regulations use the term "filed" in the context of the processing and review of new drug applications (NDAs); in the context of ANDAs, FDA uses the term "received" or "received for substantive review" to refer to the action described in the Act as filing (see 21 CFR 314.101).

¹⁷ FDAAA further clarifies that section 505(j)(5)(D)(i)(IV) gives a first applicant 30 months in which to obtain either tentative approval or approval. Section 505(q)(1)(G) of the Act, added by FDAAA, provides that as to a first applicant's ANDA, if "approval of the application was delayed because of a petition, the 30-month period under such subsection [section 505(j)(5)(D)(i)(IV)] 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 ..." (emphasis added). Thus, section 505(j)(5)(D)(i)(IV) also applies when the first applicant is eligible for a final approval, but not for a tentative approval. The absence of patent or exclusivity protection that would necessitate a tentative — rather than final — approval, does not exempt a first applicant from the requirement that it show that its application meets the scientific and technical requirements of 505(j) within 30 months of filing.

After reviewing Cobalt's ANDA, we have concluded that a change in bioequivalence requirements resulted in a delay in obtaining a tentative approval.¹⁸ Cobalt's failure to obtain a tentative approval within 30 months was caused — in part — by the agency's change in or review of the bioequivalence requirements; specifically, by a change in the reference listed drug¹⁹ against which Cobalt was to conduct its bioequivalence study. Orange Book Preface at x-xi. Throughout the relevant period, FDA identified the 100-mg strength tablet in the Orange Book as the drug product to be used in a bioequivalence study. Cobalt initially conducted its bioequivalence study using that strength of the drug, but was informed by FDA on August 8, 2006, that its in vivo bioequivalence using the 100 mg strength was not acceptable. After further study by Cobalt, it relied upon a different strength of acarbose tablets for its in vivo bioequivalence study. This change in requirements for bioequivalence data necessitated a longer review of the Cobalt ANDA.²⁰ Therefore, because FDA changed the requirements for the bioequivalence study, Cobalt did not forfeit its exclusivity pursuant to section 505(j)(5)(D)(i)(IV) of the Act.

3. The 30-Month Periods in Sections 505(j)(5)(D)(i)(I) and (IV) do not Begin to Run with Receipt of the First Applicant's Notice Letter

You assert that FDA must interpret the two 30-month periods described in the MMA forfeiture provisions as beginning not from the date the application is submitted or filed, but rather from the date the NDA holder and patent owner receive the first applicant's notice of paragraph IV certification. Cobalt's argues that this reading alone is consistent with congressional intent. We disagree. As we have stated elsewhere in this response, although there is some ambiguity created by the use of the term "submission" in section 505(j)(5)(D)(i)(I)(aa)(BB) and "filed" in section 505(j)(5)(D)(i)(IV) to identify what appears to have been intended to be the same event, that ambiguity can be easily resolved in a manner that is both consistent with the agency's use of these terms in the review of ANDAs and with the statutory scheme. You ask that we forgo this reading — one that reasonably reconciles the provisions — in favor of an interpretation entirely unmoored from statutory language. Congress, you assert, did not intend the 30-month periods to run from the date the first applicant's application is complete and FDA may begin its review; rather you would have it begin possibly months later, with receipt of notice of a paragraph IV certification.

¹⁸ Under section 505(j)(5)(D)(i)(IV), exclusivity is forfeited "unless" there has been a review of or change in requirements that has delayed approval or tentative approval of the ANDA. The statute does not permit either FDA or an ANDA applicant to comb through the ANDA review records and decide whether, had the review been conducted differently, the application could have received an approval or tentative approval before the forfeiture occurred. The review order for the very large number of ANDAs, amendments, and supplements is established through internal policies and established practice. In 2007, for example, with a total staff of approximately 210, OGD issued approval, tentative approval, not approvable, or refuse to receive letters on 1,893 ANDAs, in addition to approving or not approving 3,429 chemistry supplements. OGD does not give preferential treatment to ANDAs that are eligible for 180-day exclusivity and are, therefore, subject to the potential forfeiture of that exclusivity. To do so would draw scarce resources away from the review of other applications that may, for example, have been submitted earlier and have been waiting longer in the review queue.

¹⁹ A reference listed drug (RLD) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (see 21 CFR 314.3(b)).

²⁰ Applicants who waited to conduct their bioequivalence studies until they had received FDA's recommendations used a methodology that permitted use of the 100 mg RLD identified in the Orange Book.

You are correct that the 30-month stay period in section 505(j)(5)(B)(iii) begins with the receipt of notice of a paragraph IV certification; however, there is nothing in the statutory language or the way the stay of approval and forfeiture provisions interrelate that necessitates the significant divergence from the statutory text that you suggest. When Congress intended to measure events from the receipt of notice of paragraph IV certification, it specifically said so. Section 505(j)(5)(B)(iii) of the Act states that if a patent infringement action is initiated within the 45-day period following notice of a paragraph IV certification “the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order....” Moreover, the result of interpreting the statute as written, i.e., possibly different dates for termination of the 30-month stay and the running of a forfeiture period, are not absurd, as is suggested by Cobalt.

III. Conclusion

After consideration of the Cobalt ANDA, the applicable law, and the comprehensive and thoughtful comments submitted by interested parties, we have concluded that Cobalt was eligible for 180-day exclusivity for the '769 patent, but that exclusivity was forfeited under the failure to market forfeiture provisions at section 505(j)(5)(D)(i)(I) of the Act. Because Cobalt has forfeited 180-day exclusivity, FDA may approve any ANDA for acarbose tablets that is otherwise ready to be approved.

Sincerely,

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

Attachments

cc: Docket No. FDA-2007-P-0249
Docket No. FDA-2007-N-0445

Correspondence on 180-Day Exclusivity Issues for Acarbose Tablets

April 11, 2007: Letter from William Rakoczy to Gary Buehler, Director, Center for Drug Evaluation and Research (CDER) and Sheldon Bradshaw, Associate General Counsel/FDA Chief Counsel.

April 11, 2007: Letter from William Rakoczy to Drug Information Services Branch and Mary Ann Holovac, Director, Drug Information, CDER.

April 16, 2007: Letter from Barbara Shimel, Director, Patents & Licensing, Bayer Health Care to Mary Ann Holovac.

June 4, 2007: Letter from William Rakoczy to Elizabeth Dickinson, Office of Chief Counsel.

September 26, 2007: Letter from Gary Buehler to ANDA Applicants.

September 28, 2007: Letter from Elizabeth Ernst, Director, DRA-Multisource Products, Roxane Laboratories, Inc. to Gary Buehler.

October 8, 2007: Letter from Sean Mahoney, Intellectual Property Counsel, Upsher-Smith Laboratories, Inc. to Cecelia Parise, Office of Generic Drugs.

October 16, 2007: Letter from Marc Goshko Executive Director, Teva Parenteral Medicines to Gary Buehler.

October 17, 2007: Letter from William Rakoczy and Christine Siwik to Gary Buehler.

October 17, 2007: Letter from William Rakoczy and Christine Siwik to Gary Buehler.

October 26, 2007: Letter from Mark Shaw, Vice-President, Regulatory Affairs and Compliance, Impax Laboratories, Inc. to Gary Buehler.

November 6, 2007: Letter from William Rakoczy and Christine Siwik to Gary Buehler.

November 13, 2007: Letter from Brian Malkin, Frommer, Lawrence & Haug LLP to Cecelia Parise, Office of Generic Drugs.

December 3, 2007: Letter from Mark Shaw to Division of Dockets Management and Gary Buehler.

March 24, 2008: Letter from William Schultz and Andrew Goldfarb, Zuckerman Spaeder LLP to ANDA 78-470.

(Note: Some of these submissions were made as controlled correspondence to ANDAs that were not approved at the time of submission. Therefore they were not included in the public dockets.)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

SENT VIA TELEFAX

Reference Number: OGD #07-1254

Dear ANDA Applicant:

We are writing to solicit comment on certain legal/regulatory issues that pertain to generic drug applications for Acarbose Tablets. This letter is being sent to all applicants with pending abbreviated new drug applications (ANDAs) for Acarbose Tablets, and is being posted on FDA's web-site at <http://www.fda.gov/cder/ogd/index.htm#New>.

The reference listed drug (RLD) for Acarbose Tablets is Precose Tablets, the new drug application (NDA) held by Bayer Pharmaceuticals (Bayer). There is one patent listed for Acarbose Tablets, U.S. Patent No. 4,904,769 (the '769 patent), which expires on September 6, 2009. As you probably are aware, for it appears on the "Paragraph IV list" on FDA's website, at least one ANDA for Acarbose Tablets containing a paragraph IV certification was received by the agency on March 22, 2005. By virtue of this filing, at least one applicant became eligible for 180-day generic drug exclusivity.

As you know, the agency makes determinations regarding 180-day exclusivity only when it is in the position to either approve an application that may be eligible for 180-day exclusivity, or to act on a subsequent applicant's ANDA as to which final approval may be delayed by another application's eligibility for exclusivity.

As of the date of this letter, which is more than 30 months from March 22, 2005, no first applicant's ANDA has been approved. Also, on April 16, 2007, Bayer requested that the '769 patent be "delisted" as to Precose, i.e., they withdrew the patent information. On September 26, 2007, FDA indicated in its "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), available on FDA's website at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020482&Product_No=001&table1=OB Rx, that the request to delist this patent had been submitted on April 16, 2007.

To determine whether any ANDA referencing Precose is eligible for final approval, the agency must consider how the 180-day generic drug exclusivity forfeiture provisions at section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) apply to this set of facts. As part of the process for making such a determination, we are seeking your views regarding the applicability of sections 505(j)(5)(D)(i)(IV) -- failure to obtain tentative approval within 30 months -- and 505(j)(5)(D)(i)(I)(aa)(BB) -- failure to market by 30 months. We also are interested in your views regarding the applicability of section 505(j)(5)(D)(i)(I)(bb)(CC) -- relating to the delisting of a patent.

We are asking that you submit your comments to us by close of business on Wednesday, October 10, 2007. Please include the OGD Reference Number listed above in your correspondence.

If you have any questions regarding this correspondence, please contact Cecelia M. Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

Gary J. 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/

Robert L. West
9/26/2007 10:39:25 AM
for Gary Buehler

**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

5/7/2008 06:11:59 PM