



SENT VIA TELEFAX

Dear ANDA Applicant

Today the Food and Drug Administration (FDA or agency) approved Cobalt Pharmaceuticals' (Cobalt) and Barr Laboratories' (Barr) abbreviated new drug applications (ANDA) for Topiramate Sprinkle Capsules, 15 mg and 25 mg (Topiramate Sprinkle Capsules). Cobalt and Barr are both eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act), as in effect prior to December 8, 2003. FDA is sending you this letter as an ANDA applicant for Topiramate Sprinkle Capsules, to explain the statutory basis for Cobalt and Barr's exclusivity.

To determine whether any applicant(s) are eligible for 180-day generic drug exclusivity for Topiramate Sprinkle Capsules, the agency has had to interpret and apply an "Effective Date" provision of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173), which provides generally that the 180-day exclusivity provisions of the MMA will be effective only with respect to an ANDA filed after the date the MMA was enacted (i.e., December 8, 2003) for a listed drug for which no paragraph IV certification was made before December 8, 2003. See MMA section 1102(b)(1). FDA received ANDAs for Topiramate Sprinkle Capsules both before and after enactment of the MMA; however, the first paragraph IV certification to a patent listed for this drug product was received after enactment of the MMA. Therefore, FDA was required to determine whether to apply the pre-MMA or MMA 180-day exclusivity provisions of the Act to these ANDAs. This letter describes the reasons the agency is applying the provisions of the Act as in effect before the date of enactment of the MMA to ANDAs for Topiramate Sprinkle Capsules.

BACKGROUND

I. Patents Listed for Topiramate Sprinkle Capsules

The agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") lists the following patents for Topamax, the reference listed drug for Topiramate Sprinkle Capsules:

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
4,513,006 (the '006 patent)	September 26, 2008
5,998,380 (the '380 patent)	October 13, 2015
6,503,884 (the '884 patent)	October 13, 2015
7,018,983 (the '983 patent)	October 13, 2015
7,125,560 (the '560 patent)	March 1, 2019
7,498,311 (the '311 patent)	October 13, 2015

The '006 patent expired on September 26, 2008. The pediatric exclusivity attaching to the '006 patent expired on March 26, 2009. The '380, '884, '983 and '311 patents are method of use patents and are not at issue here.

II. ANDAs and Paragraph IV Certifications for Topiramate Sprinkle Capsules

The first ANDA referencing the listed drug Topamax was submitted before enactment of the MMA, but the first paragraph IV certification was submitted after enactment. On July 1, 2002, OGD received for filing Barr's ANDA 76-448 for Topiramate Sprinkle Capsules. At the time of submission, Barr provided a certification under section 505(j)(2)(A)(vii)(III) of the Act (a paragraph III certification) to the '006 patent. In September 2005, after enactment of the MMA, OGD received Cobalt's ANDA 77-868 for Topiramate Sprinkle Capsules. At the time of submission of its ANDA, Cobalt provided a certification under section 505(j)(2)(A)(vii)(IV) of the Act (a paragraph IV certification) to the '006 patent. Cobalt's paragraph IV certification to the '006 patent was the first paragraph IV certification to any patent for the listed drug. Cobalt and Barr both provided paragraph IV certifications to the '560 patent as of November 1, 2006.

The '006 patent has expired and thus cannot be the basis for exclusivity. There are no paragraph IV certifications to the listed method of use patents. Therefore, the only patent that could serve as a basis for 180-day exclusivity is the '560 patent (but only if the pre-MMA scheme applies).

III. Applicability of the Pre-MMA 180-day Exclusivity Provisions

The timing of these ANDA and paragraph IV submissions raises the question whether the pre-MMA or MMA 180-day exclusivity scheme applies to these drug products. Subsection (a) of section 1102 of the MMA significantly revised the 180-day generic drug provisions of section 505(j)(5)(B)(iv) the Act. The relevant "Effective Date" provision of the MMA states the following:

...the amendment made by subsection (a) shall be effective only with respect to an [ANDA] filed ... after [December 8, 2003] for a listed drug for which no [paragraph IV certification] was made before [December 8, 2003].

MMA section 1102(b)(1).

Application of this effective date provision appears straightforward in certain situations. For instance, if all ANDAs referencing a particular listed drug were submitted to FDA after December 8, 2003 (and thus no paragraph IV certification could have been submitted before December 8, 2003), the MMA 180-day exclusivity provisions would apply to all of the ANDAs. The provision also squarely addresses the situation in which at least one paragraph IV certification to a patent on the listed drug was made before December 8, 2003. In that case, all ANDAs referencing that listed drug (including ANDAs submitted after December 8, 2003) would be governed by the pre-MMA approach because the listed drug was subject to a paragraph IV certification made before the MMA was enacted. In each of these situations all ANDAs referencing the same listed drug are subject to a single statutory scheme - MMA in the first case, pre-MMA in the second. However, when one or more applications were submitted before December 8, 2003, but the first paragraph IV certification was submitted after December 8, 2003, the statutory effective date provision is ambiguous. These Topiramate Sprinkle Capsules

applications are the first instance in which the agency has had to address applicability of the effective date provision in these circumstances.¹

A threshold question is whether the same 180-day exclusivity scheme (MMA or pre-MMA) governs all ANDAs for Topiramate Sprinkle Capsules referencing the same listed drug, regardless of whether the particular application was submitted before or after December 8, 2003. Under the effective date provision, the 180-day exclusivity provisions of the MMA shall be effective only with respect to an "application" filed after December 8, 2003, for a listed drug for which no paragraph IV certification was made before December 8, 2003. Topiramate Sprinkle Capsules applications were submitted both before December 8, 2003, and after December 8, 2003, and no paragraph IV certification for the listed drug was submitted before December 8, 2003. This raises the prospect that the pre-MMA exclusivity provisions could apply to any application for Topiramate Sprinkle Capsules that was submitted before December 8, 2003 (because that is not an application filed after December 8, 2003), and the MMA provisions would apply to any application that was submitted after December 8, 2003. This outcome would not be a reasonable application of the statute.

Although both the pre-MMA and MMA exclusivity schemes are intended to provide an incentive to challenge listed patents, each has a different approach to eligibility for that exclusivity. For example, under the pre-MMA approach, an applicant could be eligible for 180-day exclusivity with respect to different patents ("patent-by-patent" exclusivity), including with respect to patent certifications to different patents submitted on different days. This exclusivity could be triggered for all patents by commercial marketing or, for a single patent, by a court decision favorable to an ANDA applicant. Section 505(j)(5)(B)(iv) of the Act (2002). There are no forfeiture provisions under the pre-MMA exclusivity approach. In contrast, under the MMA, an applicant may qualify as a "first applicant" eligible for 180-day exclusivity only with respect to patent certification submitted on the same "first" day on which any paragraph IV certification is submitted; even if an applicant is the first to certify to a later-listed patent, it will not qualify for exclusivity with respect to that patent as a result. Section 505(j)(5)(B)(iv)(II)(bb) of the Act (2008). In addition, there are a series of events that can lead to forfeiture of eligibility for exclusivity under the MMA. These include, for example, failure to obtain a timely tentative approval, and failure to market within a certain period beginning upon a patent delisting, a court decision or settlement. Section 505(j)(5)(D) of the Act (2008).

Each of these exclusivity schemes describes a distinct and coherent process under which the approval of ANDAs referencing a given listed drug may be delayed to provide a reward to the first applicant to challenge a patent. An attempt by the agency to apply both approaches to a single group of applications with a common reference listed drug could result in conflict between MMA and pre-MMA provisions (e.g., an applicant that submitted its ANDA before enactment of the MMA would claim a later-listed patent as a second basis for exclusivity while the applicant governed by the MMA could not make that claim, post-MMA applicants could claim that the MMA forfeiture provisions govern their right to obtain approval based on a forfeiture event as to

¹ Topiramate Sprinkle Capsules may be the first case in which the agency must address this question, but it is not the only set of ANDAs for which the first ANDA was submitted before December 8, 2003, and the first paragraph IV certification was submitted after December 8, 2003. This issue is also likely to arise with ANDAs referencing a number of other drugs.

the pre-MMA applicant eligible for exclusivity). Moreover, application of two different statutory schemes to applications referencing a single listed drug could result in disparate treatment of applicants, such as Cobalt and Barr, that challenge a given patent on the same day. The eligibility, triggering, and forfeiture features of the different exclusivity schemes could render one applicant ineligible for exclusivity, while the other retains its eligibility.

It is not likely that Congress intended that the pre-MMA and MMA schemes be applied in a piecemeal fashion and with a possible disparate effect on applicants simultaneously undertaking the same patent challenge. Nor is it likely that Congress intended that the transition from one approach to the other would cause unnecessary uncertainty and confusion in the industry. Accordingly, we have concluded that it is reasonable to interpret the effective date provision to impose the same statutory scheme on all applications referencing a specific listed drug. Therefore, FDA will apply a single 180-day exclusivity approach to all ANDAs for Topiramate Sprinkle Capsules.

The next matter is to determine which 180-day exclusivity regime governs these applications. As noted above, the first application for Topiramate Sprinkle Capsules was submitted before December 8, 2003, but the first paragraph IV certification was submitted after that date. The fact that the first paragraph IV certification in any application referencing the listed drug was submitted after December 8, 2003, is not dispositive, because the effective date provision directs that the MMA 180-day exclusivity provisions also only apply to applications submitted after the date of enactment.² Therefore, in this case the submission dates for both the application and for the paragraph IV certification are relevant. Because we have determined that it is appropriate to apply a single 180-day exclusivity approach to all ANDAs for Topiramate Sprinkle Capsules, we must determine whether the fact that some of these applications were submitted before enactment of the MMA warrants application of the pre-MMA exclusivity approach or whether the MMA scheme applies.

After consideration of the statutory language and the nature of each approach to exclusivity, we have concluded that it is appropriate to apply the pre-MMA statutory 180-day provisions to these applications. The effective date provision provides that, for an application referencing a listed drug - such as Topamax - for which no paragraph IV certification was submitted before enactment of the MMA, the 180-day exclusivity amendments made in the MMA shall be effective "only" with respect to an application filed after December 8, 2003. Section 1102(b)(1) of the MMA. This indicates that the agency may not be permitted to apply the MMA exclusivity provisions to an ANDA submitted before December 8, 2003. In contrast, there is no express provision prohibiting the agency from applying the pre-MMA exclusivity approach to ANDAs submitted after December 8, 2003, at least in circumstances such as these when ANDAs referencing the same listed drug were submitted both before and after December 8, 2003.

Applying the pre-MMA exclusivity approach in this situation is also reasonable in light of the fact that the date of submission of an ANDA has implications for exclusivity under the MMA that it did not have under the applicable 180-day exclusivity approach when the pre-MMA application was submitted. Under the pre-MMA approach, an ANDA applicant is under no

² Note that had Congress intended that only the date of the paragraph IV certification would be relevant, it could simply have not included the phrase "after the date of the enactment of this Act" in 1102(b)(1).

statutory obligation to obtain a tentative approval within a given time-frame to maintain any eligibility for exclusivity. In contrast, at least two of the possible forfeiture events identified in the MMA are measured from the date of submission of an applicant's ANDA. For example, the "Failure to Obtain Tentative Approval" provision at section 505(j)(5)(D)(i)(IV) of the Act directs that an ANDA applicant will, in certain circumstances, lose its eligibility for 180-day exclusivity if it fails to obtain a tentative approval within 30 months of submission of the ANDA. If FDA were to apply this forfeiture provision to ANDAs submitted well before enactment of the MMA, an ANDA applicant could find itself forfeiting exclusivity based upon a failure to meet criteria that did not exist at the time the ANDA was submitted or for much of the time the ANDA was pending (i.e., for failure to obtain a timely TA). This outcome does not appear consistent either with the effective date language or with the general principle that statutes are to be applied prospectively, unless Congress has signaled otherwise.

The effective date provisions at section 1102(b) of the MMA describe specific situations in which MMA provisions will be effective as to applications and certifications that were submitted before passage of the MMA.³ This section makes the "collusive agreements" forfeiture event described in section 505(j)(5)(D)(i)(V) of the Act (2008) applicable, regardless of when the first paragraph IV certification for a patent on the listed drug was submitted. Section 1102(b)(2) of the MMA. In addition, section 1102(b)(3) of the MMA applies the MMA definition of "decision of a court" (i.e., a final decision of a court from which no appeal ... has been or can be taken) to applications filed at any time, thus preventing an applicant that had not had its exclusivity triggered before passage of the MMA from having exclusivity triggered by a favorable district court decision that is subsequently appealed by the patent owner or NDA holder. By specifically describing the limited MMA exclusivity provisions that applied to pending applications, Congress signaled that, although the MMA amendments to the 180-day exclusivity scheme include forfeiture events that could speed the availability of generic drugs, these provisions were not to be applied to all ANDAs pending before the agency when the MMA was enacted. Instead, as discussed, section 1102(b)(1) of the MMA made the new exclusivity provisions effective only with respect to an application filed after the effective date of the MMA for a listed drug for which no paragraph IV certification was made before that date. Therefore, FDA will apply the pre-MMA 180-day exclusivity provisions to all ANDAs for Topiramate Sprinkle Capsules.

IV. Conclusion

We have determined that the pre-MMA provisions of the Act apply to all ANDAs for Topiramate Sprinkle Capsules. Under these pre-MMA exclusivity provisions at section 505(j)(5)(B)(iv) of the Act (2002), both Barr and Cobalt are eligible for 180-day exclusivity as a result of their paragraph IV certifications to the '560 patent. This exclusivity is not subject to the MMA forfeiture provisions, and may be triggered by commercial marketing or an applicable court decision.

³ We note as well that Congress expressly made certain MMA requirements for giving notice of a paragraph IV certification effective as to applications submitted on or after August 18, 2003 (almost four months before passage of the MMA). Section 1101(c) of the MMA.

If you have any questions concerning this correspondence, please contact Martin Shimer at 240-276-8419.

Sincerely yours,

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

4/15/2009 02:47:17 PM