MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 3, 2017

FROM: Martin Shimer
Deputy Director, Division of Legal and Regulatory Support
Office of Generic Drug Policy

TO: ANDA 090132

SUBJECT: 180-day Exclusivity for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg, and 80 mg

I. STATUTORY BACKGROUND

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events that can result in the forfeiture of a first applicant's[1] 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

The forfeiture provisions of the MMA appear at section 505(j)(5)(D) of the FD&C Act. Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The 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.

The "failure to obtain tentative approval" forfeiture provision establishes a bright-line rule: If within 30 months after the date of submission, an abbreviated new drug application (ANDA) has been determined by the Agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant will be given a tentative approval and will maintain eligibility for 180-day exclusivity. If tentative approval or approval[2] is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the failure [to obtain an approval] is caused by a change in or a review of the

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[1] A "first applicant" is eligible for 180-day exclusivity by virtue of submitting a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is submitted on the first day, there is only one first applicant; if two or more such ANDAs are submitted on the first day, first applicant status is shared.

[2] As explained below, *infra* note 3, FDA interprets this provision to also encompass the failure to obtain final approval, where applicable, within 30 months after the date of filing.

requirements for approval of the application imposed after the date on which the application is filed." Under this provision, it is not sufficient to show that FDA's review of the ANDA (to determine that the ANDA has met the pre-existing approval requirements), caused a failure to obtain a tentative approval or approval at 30 months. Nor is it sufficient for an applicant to show that FDA changed or reviewed (i.e., considered whether to change) the requirements for approval while the application was under review. The applicant must also show that its failure to obtain a tentative approval or approval at the 30 month date is **caused** by this change in or review of approval requirements. FDA generally will presume that the failure to obtain tentative approval or approval was caused by a change in or review of approval requirements if, at the 30 month date, the evidence demonstrates that the sponsor was actively addressing the change in or review of approval requirements (or FDA was considering such efforts), and these activities precluded tentative approval (or approval) at that time. Where the evidence fails to demonstrate that the sponsor was actively addressing the change in or review of approval requirements, and these activities precluded tentative approval (or approval) at the 30-month date, FDA generally does not presume that the failure was caused by a change in or review of approval requirements. If FDA were to hold otherwise, an applicant that receives one or more deficiencies resulting from a change in approval requirements could simply delay addressing those deficiencies and avoid forfeiture.

In addition, FDA has determined that if one of the causes of failure to get tentative approval or approval by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was filed, an applicant will not forfeit eligibility notwithstanding that there may have been other causes for failure to obtain tentative approval or approval by the 30-month forfeiture date. Thus, to find non-forfeiture, FDA must find that acceptability of at least one aspect of the ANDA (e.g., chemistry) was delayed, and that this delay was caused at least in part, by a change in or review of the requirements for approval (which the sponsor or FDA is actively addressing), irrespective of what other elements may also have been outstanding at the 30-month date. In other words, "but-for" causation is not required in order to qualify for this exception. FDA has determined that this interpretation best effectuates the policy embodied in the exception. It does not penalize applicants for reviews of or changes in approval requirements imposed on applicants after their ANDAs are filed that are a cause of the failure to obtain approvals or tentative approvals within 30 months (and presumes causation if, at the 30 month date, the sponsor was actively addressing those changes, and these changes precluded approval), and continues to incentivize applicants to challenge patents by preserving in many instances the opportunity to obtain 180-day exclusivity.

Under this provision, the 30-month timeframe is generally measured without regard to the length of time the ANDA was under review by the Agency. However, section 505(q)(1)(G) of the FD&C Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85) provides one exception. This section provides that

> If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and 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), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Thus, pursuant to this provision, if approval was delayed because of a 505(q) petition such that the application was not ready to be approved at 30 months from the date of submission because of the time it took the Agency to respond to the 505(q) petition, the 30-month-period-from-initial-submission deadline for obtaining a tentative (or final) approval will be extended by the amount of time that the 505(q) petition was under review.[3]

II. DISCUSSION

Mutual Pharmaceutical Company, Inc. (Mutual) submitted ANDA 090132 for Carvedilol Phosphate Extended-Release Capsules, 80 mg on November 19, 2007. On December 21, 2007, Mutual submitted a new strength amendment to ANDA 090132, which provides for the addition of the 40 mg strength of the product. On March 18, 2008, Mutual submitted another new strength amendment to ANDA 090132, which provides for the addition of the 10 mg and 20 mg strengths of the product. Mutual qualified as a "first applicant" for all strengths, and therefore is eligible for 180-day exclusivity for its generic Carvedilol Phosphate Extended-Release Capsule product absent forfeiture.[4]

Mutual had 30 months to obtain tentative approval or approval for the purposes of section 505(j)(5)(D)(i)(IV) of the Act. Thirty months from the submission of the original ANDA containing the 80 mg strength is May 19, 2010. Thirty months from the submission of the new strength amendment for the 40 mg strength is June 21, 2010. Thirty months from the submission of the new strength amendment for the 10 and 20 mg strengths is September 18, 2010.

This memorandum addresses whether Mutual has forfeited its eligibility for 180-day exclusivity

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[3] In addition to tolling the 30-month period described in 505(j)(5)(D)(i)(IV) in certain circumstances where a petition is under review, section 505(q)(1)(G) clarified the scope of section 505(j)(5)(D)(i)(IV). If the phrase "tentative approval" in section 505(j)(5)(D)(i)(IV) is viewed in isolation, it might be suggested that this section applies only when an ANDA is eligible for a tentative approval due to a patent, 30-month stay or exclusivity blocking final approval, and that this provision cannot serve as a basis for forfeiture when an ANDA would have otherwise been eligible only for a *final* approval because there is no blocking patent, 30-month stay or exclusivity. Although section 505(j)(5)(D)(i)(IV) refers to "tentative approvals," the terms of section 505(q)(1)(G) clearly describe a broader scope. Section 505(q)(1)(G) expressly states that if "approval" of the first applicant's application was delayed because of a petition, the 30-month period described in section 505(j)(5)(D)(i)(IV) will be extended. Thus, Congress contemplated that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which an ANDA generally must obtain either tentative approval or final approval. This interpretation squares both with the statutory language and with not permitting the 180-day exclusivity for a first applicant whose ANDA is deficient to delay approval of subsequent applications. Therefore, FDA interprets section 505(j)(5)(D)(i)(IV) as requiring that, unless the period is extended for one of the reasons described in the FD&C Act, a first applicant that fails to obtain either tentative approval or approval for its ANDA within 30 months will forfeit eligibility for 180-day exclusivity.

[4] We note that on July 12, 2016, Sun Pharmaceuticals Industries, Inc. notified FDA that it was the new applicant for ANDA 090132. FDA acknowledged receipt of this communication on July 22, 2016.

due to its failure to obtain tentative approval or approval by the thirty month dates identified above.

Axinn Veltrop & Harkrider LLP (Axinn), counsel for Mutual, submitted multiple correspondence supporting its assertion that Mutual did not forfeit its eligibility for 180-day exclusivity even though its ANDA was not tentatively approved within 30 months of filing.[5] We note that ANDA applicants frequently submit correspondence related to forfeiture of 180-day exclusivity. Although FDA does not expect or require such correspondence, the Agency will consider any submitted correspondence when making a forfeiture decision. However, because we have found that Mutual's failure to obtain tentative approval was caused by a change in the requirements for approval as described below, we have not addressed all of Mutual's assertions here.

We must base our forfeiture analysis on the record before the Agency. The following is a timeline of certain key submissions and actions regarding ANDA 090132:

11/19/2007	ANDA submitted (80 mg)
12/21/2007	New strength amendment (40 mg)
3/18/2008	New strength amendment (20 mg and 10 mg)
4/22/2008	Request for telephone amendment (product quality)
5/5/2008	Amendment (product quality) (telephone)
5/5/2008	Bioequivalence review (dissolution) (deficient)
5/13/2008	Bioequivalence deficiencies facsimile (dissolution)
6/20/2008	Request for telephone amendment (exclusivity, product quality)
6/25/2008	Amendment (exclusivity, product quality) (telephone)
7/9/2008	Request for telephone amendment (product quality)
7/24/2008	Amendment (product quality) (telephone)
8/1/2008	Request for telephone amendment (quality)
8/8/2008	Amendment (product quality) (telephone)
8/14/2008	Amendment (bioequivalence (dissolution))
8/8/2008	Amendment (product quality)
10/8/2008	Bioequivalence review (dissolution) (deficient)
10/23/2008	Bioequivalence deficiencies facsimile (dissolution)
12/3/2008	Amendment (bioequivalence (dissolution))

[5] Letter to K. Webber (OGD) from C. Landmon (Axinn) re: "Mutual Pharmaceutical Company's ANDA No. 90-132 for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg and 80 mg" (May 17, 2010); Letter to K. Webber (OGD) from C. Landmon (Axion) re: "Mutual Pharmaceutical Company's ANDA No. 90-132 for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg and 80 mg" (October 25, 2010); Letter to K. Webber (OGD) from C. Landmon (Axion) re: "Mutual Pharmaceutical Company's ANDA No. 90-132 for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg and 80 mg" (November 18, 2010); Letter to K. Webber (OGD) from C. Landmon (Axion) re: "Mutual Pharmaceutical Company's ANDA No. 90-132 for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg and 80 mg" (February 14, 2011); Letter to G. Geba (OGD) from C. Landmon (Axion) re: "Mutual Pharmaceutical Company's ANDA No. 90-132 for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg and 80 mg" (November 13, 2012).

1/5/2009	Bioequivalence review (dissolution) (deficient)
1/5/2009	Request for telephone amendment (product quality)
1/6/2009	Bioequivalence deficiencies facsimile (dissolution)
1/9/2009	Bioequivalence deficiencies facsimile (dissolution)
1/26/2009	Amendment (bioequivalence (dissolution))
2/5/2009	Amendment (product quality) (telephone)
5/5/2009	Amendment (bioequivalence (dissolution))
5/11/2009	Amendment (labeling)
7/13/2009	Bioequivalence review (deficient)
7/16/2009	Bioequivalence deficiencies facsimile
8/28/2009	Amendment (labeling)
10/19/2009	Telephone request for samples
11/2/2009	Amendment (samples)
11/30/2009	Labeling review (deficient)
11/30/2009	Labeling deficiencies facsimile
1/22/2010	Amendment (labeling)
2/2010	*Publication of draft product specific guidance*
4/19/2010	*Citizen petition submitted*
5/13/2010	Email correspondence regarding 180-day exclusivity
5/14/2010	Amendment (bioequivalence, labeling, product quality)
5/18/2010	Amendment (bioequivalence, product quality)
5/19/2010	*Correspondence from OGD regarding 180-day exclusivity*[6]
5/19/2010	**11/19/2007 plus 30 months (80 mg)**
5/25/2010[7]	5/17/ 2010 correspondence regarding 180-day exclusivity
5/25/2010[8]	5/20/ 2010 correspondence regarding 180-day exclusivity
6/18/2010	Product quality review (deficient)
6/21/2010	**12/21/2007 plus 30 months (40 mg)**
6/25/2010	Product quality review (deficient)
6/25/2010	Product quality deficiencies facsimile
9/2/2010	Amendment (product quality)
9/18/2010	**3/18/2008 plus 30 months (20 mg and 10 mg)**
10/15/2010	*Citizen petition answered*
10/18/2010	Product quality review (deficient)
10/18/2010	Product quality deficiencies facsimile
10/25/2010	Correspondence regarding 180-day exclusivity
11/5/2010	Meeting request (product quality, bioequivalence)
11/19/2010	11/18/2010 correspondence regarding 180-day exclusivity
12/2/2010	Amendment (bioequivalence, product quality)
2/15/2011	2/14/2011 correspondence regarding 180-day exclusivity

[6] The correspondence from the Agency indicated that "since your ANDA was filed in November 2007, FDA has been reviewing the requirements for ANDAs referencing Coreg CR."

[7] This reflects the date the correspondence was received by FDA.

[8] This reflects the date the correspondence was received by FDA.

3/1/2011	Internal Meeting (3/30/2011 meeting minutes)
3/8/2011	Clinical review (deficient)
3/16/2011	Bioequivalence review (deficient)
3/22/2011	Bioequivalence deficiencies facsimile
11/14/2012	11/13/2012 correspondence regarding 180-day exclusivity
3/1/2013	Amendment (bioequivalence)
4/26/2013	Labeling review (deficient)
5/22/2013	Amendment (bioequivalence)
8/29/2013	Amendment (withdraw facility)
12/16/2013	Request for telephone amendment (product quality)
12/19/2013	Amendment (product quality) (telephone)
1/2/2014	Bioequivalence review (deficient)
1/3/2014	OSI consult request for biopharmaceutical inspections
1/17/2014	12/20/2013 correspondence
1/30/2014	Memo requesting for-cause inspection for bioequivalence studies
1/30/2014	Product quality review (adequate)
1/30/2014	Complete response letter (bioequivalence, labeling)
2/18/2014	Meeting request (bioequivalence)
3/26/2014	Meeting request granted
4/24/2014	(internal) Post-CR meeting request written responses
4/28/2014	Post-CR meeting request written responses
7/30/2014	Complete response (bioequivalence, labeling)
1/30/2015	Easily correctable deficiency response (bioequivalence)
2/5/2015	Easily correctable deficiency response (labeling)
2/20/2015	Bioequivalence review (adequate)
4/20/2015	Easily correctable deficiency response (labeling)
6/8/2015	Labeling review (adequate)
6/12/2015	Easily correctable deficiency (labeling)
8/13/2015	Complete response (cGMP)
9/9/2016	Request for extension to respond to CR letter
9/27/2016	Extension to respond to CR letter granted
2/24/2017	Post CR meeting request
3/27/2017	Meeting request granted – written responses only
4/27/2017	Meeting request written responses
5/9/2017	Complete response (cGMP)
7/9/2017	Easily correctable deficiency (labeling)
7/24/2017	Easily correctable deficiency response (labeling)
7/28/2017	Information request (product quality)
7/28/2017	Information request response (product quality)
8/1/2017	Chemistry review (adequate)
8/2/2017	Bioequivalence review (adequate)
8/4/2017	Labeling review (adequate)

On April 19, 2010, Frommer Lawrence & Haug LLP submitted a citizen petition (Docket No. FDA-2010-P-0216) on behalf of Flamel Technologies, S.A. requesting that FDA require any ANDA or section 505(b)(2) NDA that references Coreg (Carvedilol Phosphate) Extended-Release Capsules to include test results demonstrating bioequivalence for the pharmacokinetic parameter C_{min} in addition to traditional pharmacokinetic parameters. FDA responded to the petition on October 15, 2010. There is no evidence that FDA's consideration of this petition, itself, caused a delay in approval or tentative approval of Mutual's ANDA. Accordingly, the 30-month periods for tentative approval were not extended under section 505(q)(1)(G) of the FD&C Act.

FDA Review of ANDA 090132

As the above timeline indicates, at the 30-month forfeiture dates for this ANDA (i.e., May 19, 2010, June 21, 2010, and September 18, 2010), bioequivalence, product quality, and labeling were deficient. However, as discussed below, FDA has identified a change in the requirements for approval regarding bioequivalence and has concluded that this change in the approval requirements was a cause of Mutual's failure to obtain tentative approval by the 30-month forfeiture dates for this ANDA.

Bioequivalence Review

At the time ANDA 090132 was submitted, FDA did not require that applicants conduct dissolution testing using ethanol for ANDAs for modified-release drug products.[9] In February 2010, after the submission of ANDA 090132 but several months prior to the 30-month forfeiture dates for this ANDA, the Agency published a draft product-specific guidance for Carvedilol Phosphate Extended Release Capsules (referencing NDA 022012, Coreg CR (Carvedilol Phosphate) Extended Release Capsules, 10 mg, 20 mg, 40 mg, and 80 mg).[10] Due to concerns of dose dumping from this drug product when taken with alcohol, the draft product-specific guidance stated that applicants should also conduct dissolution testing using various concentrations of ethanol in the dissolution medium.[11] On May 14, 2010, approximately three months after the publication of the draft product-specific guidance and prior to the 30-month forfeiture dates for this ANDA, Mutual submitted an amendment which purported to address the new dissolution testing described in the Agency's draft product-specific guidance for Carvedilol Phosphate Extended Release Capsules. At the 30-month forfeiture dates for this ANDA, the dissolution data for ANDA 090132 was still under review. The Agency found the dissolution testing adequate on March 16, 2011.[12]

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[9] See, e.g., FDA's Guidance for Industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Revision 1) (March 2003), at 11, available at https://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf.

[10] FDA's Draft Guidance on Carvedilol Phosphate, Recommended February 2010, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199626.pdf (February 2010 draft product specific guidance).

[11] Id.

[12] Division of Bioequivalence Review for ANDA 090132 (March 16, 2011), at 2.

We conclude that there was a change in the requirements for approval with respect to bioequivalence, as outlined above, and that this change was a cause of Mutual's failure to obtain tentative approval by the forfeiture dates. After the submission of Mutual's ANDA, in the February 2010 draft product-specific guidance, the Agency advised applicants to conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium for Carvedilol Phosphate Extended Release Capsules. Mutual actively addressed this change in the requirements for approval before the 30-month forfeiture dates for this ANDA when it submitted its May 14, 2010 amendment containing information to address the new dissolution testing described in the February 2010 draft product-specific guidance. As of the 30-month forfeiture dates for this ANDA, the Agency was still reviewing Mutual's dissolution information. Based on these facts (including, among other things, that Mutual had been actively addressing the change in approval requirements and that FDA was reviewing Mutual's efforts at the 30-month forfeiture dates), we conclude that the requirement to comply with the new dissolution testing using various concentrations of ethanol in the dissolution medium was a cause of Mutual's failure to obtain tentative approval by the forfeiture date.

Product Quality and Labeling Reviews

Because FDA has determined that there was a change in the approval requirements with respect to bioequivalence, which was a cause of Mutual's failure to obtain tentative approval by May 19, 2010, June 21, 2010, and September 18, 2010, we need not determine whether there is a separate basis for non-forfeiture with respect to product quality or labeling.

III. CONCLUSION

Mutual's ANDA for Carvedilol Phosphate Extended-Release Capsules was submitted on November 19, 2007 for the 80 mg strength, December 21, 2007 for the 40 mg strength, and March 18, 2008 for the 10 and 20 mg strengths. The 30-month forfeiture date was May 19, 2010 for the 80 mg strength, June 21, 2010 for the 40 mg strength, and September 18, 2010 for the 10 and 20 mg strengths. Mutual's ANDA was not tentatively approved within these time periods. The Agency finds that Mutual's failure to obtain tentative approval was caused by a change in the requirements for approval, specifically to conduct dissolution testing using various concentrations of ethanol in the dissolution medium as described in the February 2010 draft product-specific guidance. We therefore conclude that Mutual has not forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the FD&C Act for Carvedilol Phosphate Extended-Release Capsules, 10 mg, 20 mg, 40 mg, and 80 mg.

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