MEMORANDUM

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

---

DATE: October 25, 2017

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

TO: ANDA 091640

SUBJECT: 180-day Exclusivity for Mesalamine Delayed-Release Tablets USP, 1.2 g

## 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[2] 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

---

[1] A "first applicant" is eligible for 180-day exclusivity by virtue of filing 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 filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

[2] For applications submitted between January 9, 2010, and July 9, 2012 containing a Paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on September 30, 2015, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months. For applications submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on October 1, 2015, and ending on September 30, 2016, section 1133 of FDASIA extends this period to 36 months. In addition, if an application was submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and FDA has not approved or tentatively approved the application but must consider whether the applicant has forfeited exclusivity because a potentially blocked application is ready for approval, FDA will apply the 36-month period if it makes the forfeiture determination between the period of time beginning on October 1, 2015, and ending on September 30, 2016. For all other applications, the 30-month period set forth in FD&C Act section 505(j)(5)(D)(i)(IV) applies.

on which the application is filed.

The "failure to obtain tentative approval" forfeiture provision establishes a bright-line rule: If within 30 months 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[3] 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 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 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

[3] As explained below in note 4, FDA interprets this provision to also encompass the failure to obtain final approval, where applicable, within 30 months of filing.

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, subsection 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 subsection 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.[4]

## II. DISCUSSION

Zydus Pharmaceuticals (USA), Inc. (Zydus) submitted ANDA 091640 for Mesalamine Delayed-Release Tablets USP, 1.2 g, on December 16, 2009. ANDA 091640 references Lialda (Mesalamine) Delayed-Release Tablets, 1200 mg, (new drug application (NDA) 022000) as its reference listed drug (RLD). Zydus qualified as a "first applicant" for Mesalamine Delayed-Release Tablets and, therefore, was eligible for 180-day exclusivity absent forfeiture. Thirty

[4] 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.

months from the submission of the ANDA was June 16, 2012. As of that date, Zydus had not received tentative approval of its ANDA.

This memorandum addresses whether Zydus has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by June 16, 2012.

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 091640:

| | |
|---|---|
| 9/10/2008 | Citizen Petition submitted (Docket No. FDA-2008-P-0507) |
| 12/16/2009 | ANDA submitted |
| 2/22/2010 | Citizen Petition submitted (Docket No. FDA-2010-P-0111) |
| 5/27/2010 | Filing Receipt |
| 7/28/2010 | Bioequivalence (Dissolution) Review (deficient) |
| 8/3/2010 | Bioequivalence Deficiencies (dissolution deficiencies) |
| 8/20/2010 | Citizen Petition Response (Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507) |
| 9/9/2010 | Bioequivalence Dissolution Acknowledgment |
| 12/3/2010 | Chemistry Review (deficient) |
| 12/3/2010 | Quality Deficiency – Minor |
| 1/28/2011 | Bioequivalency (Clinical) Information Request |
| 2/14/2011 | Quality Minor Amendment / Response to Information Request |
| 3/22/2011 | Clinical Bioequivalency Amendment |
| 4/15/2011 | Bioequivalency (Clinical) Information Request |
| 4/28/2011 | Labeling Review (deficient) |
| 5/2/2011 | Labeling Comments (labeling deficiencies) |
| 5/11/2011 | Clinical Bioequivalency Amendment |
| 5/19/2011 | Labeling Amendment |
| 6/1/2011 | Chemistry Review (deficient) |
| 6/1/2011 | Quality Deficiency – Minor |
| 9/29/2011 | Labeling Amendment |
| 2/23/2012 | Bioequivalence Review (deficient) |
| **3/13/2012** | **Bioequivalence Comments (bioequivalence deficiencies)** |
| ***6/16/2012*** | ***12/16/2009 plus 30 months*** |
| 6/25/2012 | Quality Minor Amendment / Response to Information Request |
| 7/2/2012 | Labeling Amendment |
| 7/13/2012 | Labeling Review (deficient) |
| 7/16/2012 | Labeling Comments (labeling deficiencies) |
| 7/19/2012 | Quality Minor Amendment |
| 8/18/2012 | Labeling Amendment |
| 8/21/2012 | Chemistry Review (deficient) |
| 8/21/2012 | Quality Deficiency – Minor |

| | |
|---|---|
| 9/19/2012 | Labeling Review (acceptable) |
| 10/23/2012 | Quality Minor Amendment / Response to Information Request |
| 2/26/2013 | Chemistry Review (deficient) |
| **3/13/2013** | **Complete Response Letter (Product Quality, Bioequivalence)** |
| **10/23/2013** | **Complete Response (Product Quality, Bioequivalence)** |

Zydus has not submitted any correspondence regarding its eligibility for 180-day exclusivity.[5]

Two citizen petitions were submitted about mesalamine delayed-release products, one before Zydus's ANDA submission and one after it.[6] FDA responded to both petitions together on August 20, 2010. One of the citizen petitions, Citizen Petition Docket No. FDA-2010-P-0111, was subject to section 505(q) of the FD&C Act. As noted in the timeline above, it was answered over one-and-a-half years before FDA notified Zydus of bioequivalence deficiencies in its application. There is no evidence that FDA's consideration of this petition, itself, caused a delay in approval or tentative approval. Accordingly, the 30-month period for tentative approval was not extended past June 16, 2012 under section 505(q)(1)(G) of the FD&C Act.

**FDA Review of ANDA 091640**

As the above timeline indicates, at the 30-month forfeiture date of June 16, 2012, bioequivalence, chemistry, and labeling were deficient.

**Bioequivalence Review**

FDA reviewed Zydus's clinical endpoint study for ANDA 091640 on February 23, 2012 and determined that the information submitted was inadequate to demonstrate bioequivalence.[7] Deficiencies identified in this review were first communicated to Zydus in the Agency's March 13, 2012 Bioequivalence Comments for ANDA 091640.[8] At the 30-month forfeiture date of June 16, 2012, Zydus had not yet adequately responded to these bioequivalence deficiencies.

---

[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.

[6] These two citizen petitions raised similar issues regarding how applicants for generic formulations of extended- or delayed-release orally administered mesalamine drug products should show bioequivalence to certain NDAs for mesalamine extended-release products (Asacol and Pentasa) (Letter from Dr. Janet Woodcock, Director, CDER, FDA, to Izumi Hara, Warner Chilcott Company, LLC and Jeffrey Jonas, Shire Pharmaceuticals, Inc. re: Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507, at 1 (Citizen Petition Response)). Although they relate to different RLDs than that used by Zydus in its ANDA, for completeness, we consider them here.

[7] ANDA 091640, Division of Bioequivalence Review (February 23, 2012).

[8] Facsimile from Chitra Mahadevan (OGD) to G. Srinivas (Zydus) re: "Bioequivalence Amendment ANDA 091640" (March 13, 2012) (March 13, 2012 Bioequivalence Comments).

One of the deficiencies identified in the Agency's March 13, 2012 Bioequivalence Comments noted a change in bioequivalence methodology that was consistent with FDA's response to Citizen Petition Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507.[9] Specifically, the deficiency noted that, as described in the citizen petition response, a bioequivalence study with clinical endpoints was no longer considered to be sufficiently sensitive to establish bioequivalence of mesalamine delayed-release tablets and that applicants for this product should demonstrate bioequivalence using data from comparative pharmacokinetic (PK) studies and in vitro dissolution studies.[10] Accordingly, Zydus was advised to conduct PK studies comparing its test product to the reference product under both fasting and fed conditions.[11]

FDA's Citizen Petition Response to Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507 was published on August 20, 2010, eight months after the submission of ANDA 091640. Prior to the Citizen Petition Response, FDA recommended that comparative clinical endpoint studies, rather than PK studies, should be used (along with in vitro dissolution studies) to show bioequivalence in orally administered extended release or delayed-release mesalamine drugs.[12] However, in light of new data from PK and comparative clinical endpoint studies in modified-release mesalamine products, as well as recent developments in regulatory science concerning the analysis of PK data, the Agency stated in the Citizen Petition Response that it no longer recommends comparative clinical endpoint studies to show bioequivalence for these products.[13] Rather, FDA concluded that applicants should show bioequivalence to certain NDAs for mesalamine extended-release products (Asacol and Pentasa) through a combination of PK studies and in vitro dissolution testing.[14] In its February 23, 2012 bioequivalence review for ANDA 091640, FDA determined that the principles described in the Citizen Petition Response should apply to generic versions of Lialda as well and that Zydus must conduct comparative PK studies (under both fasting and fed conditions) and in vitro dissolution studies to demonstrate bioequivalence instead of the in vivo studies Zydus had previously conducted. This change in bioequivalence requirements for approval, which required Zydus to plan and conduct additional studies, was first communicated to Zydus as Bioequivalence Comments on March 13, 2012,[15] three months before the forfeiture date of June 16, 2012 for ANDA 091640. Zydus later received a Complete Response Letter for this ANDA on March 13, 2013,[16] which included the same bioequivalence deficiencies communicated in the Agency's March 13, 2012 Bioequivalence Comments. The Complete Response Letter also stated that "a partial response to this letter will not be processed as a resubmission and will not start a new review cycle."[17]

---

[9] Id.
[10] Id.
[11] Id.
[12] Citizen Petition Response, at 7, citing Letter from Dale P. Conner (OGD) to Lawrence & Haug LLP (September 11, 2007).
[13] Id., at 8.
[14] Id.
[15] March 13, 2012 Bioequivalence Comments, supra n.9.
[16] Correspondence from G. Geba (OGD) to G. Srinivas (Zydus) re: "ANDA 091640 Complete Response" (March 13, 2013) (Complete Response Letter).
[17] Id., at 3.

On October 23, 2013, Zydus responded to the Agency's March 13, 2013 Complete Response Letter,[18] which included information to address the bioequivalence deficiencies communicated in the Agency's March 13, 2012 Bioequivalence Comments and March 13, 2013 Complete Response Letter for ANDA 091640. A review of this information shows that Zydus's application was not ready for approval at the forfeiture date due, in part, to the fact that while Zydus's application was pending there was a change in the bioequivalence studies expected for approval. At the time of the forfeiture date of June 16, 2012, Zydus was actively addressing the bioequivalence deficiencies described above and communicated to Zydus in the March 13, 2012 Bioequivalence Comments, and Zydus had not yet demonstrated bioequivalence under the new methodology as of the June 16, 2012 forfeiture date. Specifically, Zydus conducted a fasting PK study,[19] a fed PK study,[20] and in vitro dissolution studies[21] before the June 16, 2012 forfeiture date. However, Zydus determined that it had to repeat the fed PK study because the results did not support bioequivalence.[22] Accordingly, Zydus conducted its second fed PK study for ANDA 091640 in September 2012.[23] The results of the second fed PK study also did not support bioequivalence.[24] Therefore, Zydus conducted its third fed PK study for ANDA 091640 in April/May 2013,[25] after it had received a Complete Response Letter for the ANDA. In its October 23, 2013 Complete Response, Zydus submitted the results of the new fasting and fed PK studies and in vitro dissolution studies, including information and results related to the failed fed PK studies it had also conducted, along with other information to address all the deficiencies in the Agency's March 13, 2013 Complete Response Letter.

Based on these facts, we conclude that Zydus failed to obtain tentative approval within 30 months and this failure was caused by a change in the requirements for approval. As described above, Zydus was actively addressing the change at the forfeiture date. We conclude that Zydus's efforts to comply with the new bioequivalence methodology for modified-release

---

[18] ANDA 091640, Sequence 0020 (October 23, 2013) (Resubmission).
[19] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pivotal-be-summary.pdf, "Table 10: Study Information (Fasting Study)" (October 23, 2013) (study number MSN-P2-480 dosing dates April 29, 2012 (period 1) – May 13, 2012 (period 3)).
[20] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pilot-be-summary-msn-p2-481, "Table 10: Study Information" (October 23, 2013) (study number MSN-P2-481 dosing dates May 10, 2012 (period 1) – May 24, 2012 (period 3)).
[21] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pivotal-be-summary.pdf, "Table 5: Summary of In Vitro Dissolution Studies" (October 23, 2013) (testing dates March 25, 2012 and April 13, 2012).
[22] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pilot-be-summary-msn-p2-481, "Table 3b: Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE studies" (October 23, 2013) (reporting $C_{max}$ outcome as "not bioequivalent").
[23] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pilot-be-summary-msn-p2-602, "Table 10: Study Information" (October 23, 2013) (study number MSN-P2-602 dosing dates September 5, 2012 (period 1) – September 19, 2012 (period 3)).
[24] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pilot-be-summary-msn-p2-602, "Table 3b: Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE studies" (October 23, 2013) (reporting $LC_{max}$ outcome as "not bioequivalent").
[25] ANDA 091640, Sequence 0020, Module 2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, pivotal-be-summary.pdf, "Table 10: Study Information (Fed Study)" (October 23, 2013) (study number MSN-P2-482 dosing dates April 22, 2013 (period 1) – May 6, 2013 (period 3)).

mesalamine products, which methodology was revised while Zydus's application was pending, was a cause of its failure to obtain tentative approval by the June 16, 2012 forfeiture date.

**Chemistry and Labeling Review**

Because FDA has determined that there was a change in the approval requirements with respect to bioequivalence, which was a cause of Zydus's failure to obtain tentative approval by the June 16, 2012 forfeiture date, we need not determine whether there is a separate basis for non-forfeiture with respect to chemistry or labeling.

## III.CONCLUSION

Zydus's ANDA 091640 for Mesalamine Delayed-Release Tablets USP, 1.2 g, was submitted on December 16, 2009. Thirty months after this date was June 16, 2012. Zydus's ANDA was not tentatively approved within this period. However, FDA concludes that there was a change in the requirements for approval with respect to bioequivalence, which was a cause of Zydus's failure to obtain tentative approval by the 30-month forfeiture date of June 16, 2012. Therefore, Zydus 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 Mesalamine Delayed-Release Tablets USP, 1.2 g.

Martin H. Shimer Ii -S

Digitally signed by Martin H. Shimer Ii -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300157630, cn=Martin H. Shimer Ii -S
Date: 2017.10.25 10:59:24 -04'00'