M E M O R A N D U M

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

DATE: September 28, 2012

FROM: Martin Shimer
Branch Chief, Regulatory Support Branch, Office of Generic Drugs (HFD-600)

TO: ANDA 077492

SUBJECT: 180-day Exclusivity for Valsartan Tablets, 40 mg, 80 mg, 160 mg, and 320 mg

I. STATUTORY BACKGROUND

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events which 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 Act).

The forfeiture provisions of the MMA now appear at section 505(j)(5)(D) of the 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 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 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

[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, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months. However, because this application was not submitted during the relevant time period, that extension is inapplicable here.

180-day exclusivity. If tentative approval is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the failure to obtain tentative 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 changed or reviewed 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 – that is, one or more issues holding up tentative approval at the 30 month date must be causally connected to the approval requirements that FDA reviewed or changed.

"But-for" causation is not required in order to qualify for this exception. If one of the causes of failure to get tentative 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 even if there were other causes for failure to obtain tentative approval by the 30-month forfeiture date that were not caused by a change in or review of the requirements for approval. Thus, to avoid forfeiture, an applicant need only show that acceptability of one aspect of the ANDA (e.g., chemistry) was delayed due to a change in or review of the requirements for approval, irrespective of what other elements may also have been outstanding at the 30-month date. 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 cause the failure to obtain approvals or tentative approvals within 30-months 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, new subsection 505(q)(1)(G) of the 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 tentative (or final) approval was delayed because of a 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 petition, the 30-month-period-from-initial-submission deadline for obtaining a tentative (or final) approval will be extended by the

amount of time during which the petition was under review.[3]

II. DISCUSSION

Ranbaxy Laboratories Limited (Ranbaxy) filed ANDA 077492 for Valsartan Tablets, 40 mg, 80 mg, 160 mg, and 320 mg, on December 28, 2004. Ranbaxy qualified as a "first applicant" on all strengths and therefore was eligible for 180-day exclusivity for all strengths of its generic Valsartan Tablets. Thirty months from the submission of the ANDA was June 28, 2007. As of that date, Ranbaxy had not received tentative approval of its ANDA. Mylan Laboratories Ltd. (Mylan), a subsequent applicant potentially blocked by Ranbaxy's exclusivity, has submitted three letters to FDA asserting that Ranbaxy has failed to obtain tentative approval by the 30-month forfeiture date, and that there has been no change in or review of the requirements for approval subsequent to submission of the ANDA on which an exception to forfeiture could be based. This memorandum addresses whether Ranbaxy has forfeited its eligibility for the 180-day exclusivity due to its failure to obtain tentative approval by June 28, 2007.[4]

The following is a timeline of ANDA 077492:

12/28/2004	ANDA filed
4/11/2005	Bioequivalence dissolution deficiencies faxed
4/20/2005	Bioequivalence amendment
5/11/2005	Labeling review (deficient)
5/26/2005	Labeling deficiencies faxed
6/21/2005	Labeling amendment
6/24/2005	Chemistry review #1 (deficient); chemistry deficiencies faxed
8/3/2005	Reference listed drug (RLD) labeling revisions approved
12/22/2005	Chemistry amendment
1/17/2006	Labeling review (deficient)

[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 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 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 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] To note, no citizen petition was filed subject to 505(q) of the Act.

1/19/2006	Labeling deficiencies faxed
1/20/2006	Bioequivalence amendment
1/25/2006	Patent amendment; labeling amendment
2/1/2006	Bioequivalence review (acceptable)
4/5/2006	Labeling review (acceptable)
5/4/2006	Chemistry t-con
5/10/2006	Chemistry t-con amendment
11/22/2006	RLD labeling revisions approved.
5/1/2007	New official United States Pharmacopeia (USP) monograph on Valsartan
6/18/2007	Chemistry amendment (revised stability data)
6/21/2007	T-con (asked to submit revised labeling)
6/25/2007	Labeling amendment
6/27/2007	Chemistry amendment
6/28/2007	***12/28/2004 plus 30 months***
7/2/2007	Chemistry t-con
7/3/2007	Labeling review (acceptable)
7/5/2007	Chemistry t-con amendment
9/17/2007	Chemistry amendment (revised stability data)
10/25/2007	Tentative approval
2/5/2008	Chemistry review #2 (acceptable)
2/25/2009	AIP letter sent from CDER. AIP invoked.
2/8/2011	Email to firm requesting drug product samples
2/25/2011	Chemistry amendment
5/19/2011	Chemistry amendment
10/3/2011	Chemistry amendment; bioequivalence amendment
1/26/2012	Consent Decree entered regarding AIP issues.
2/27/2012	Correspondence
3/23/2012	Tablet size memo
4/10/2012	Labeling amendment
5/4/2012	Substantially complete memo; substantially complete letter sent
5/8/2012	Substantially complete filing checklist
5/14/2012	Labeling review (acceptable)
7/6/2012	AIP revoked for this ANDA
7/13/2012	Chemistry amendment (to withdraw Paonta Sahib site)
7/16/2012	Chemistry amendment (request for final approval)
7/19/2012	Chemistry amendment
8/6/2012	Chemistry t-con
8/8/2012	Labeling t-con
8/13/2012	Bioequivalence t-con
8/15/2012	Labeling amendment

8/20/2012	Chemistry amendment
8/22/2012	Chemistry t-con

FDA Review of ANDA 077492

As the above timeline indicates, bioequivalence was found acceptable on February 1, 2006, and was the only review discipline that was acceptable at the "30-month forfeiture date" of June 28, 2007. Approximately five days after the 30-month forfeiture date, the labeling review was found acceptable. Chemistry was not found acceptable until approximately four months after the 30-month forfeiture date.

Ranbaxy has not submitted any correspondence regarding the company's failure to obtain tentative approval by June 28, 2007. Ranbaxy's silence may be attributable to the fact that FDA's October 25, 2007 letter tentatively approving Ranbaxy's application stated, "[t]his letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act, except to note that for purposes of sections 505(j)(5)(B)(iv) and 505(j)(5)(D)(i)(IV), the Agency regards the change in the USP monograph for Valsartan, published on May 1, 2007, in response to which you submitted an amendment on June 17, 2007, to be a change in the requirements for approval imposed after the date on which your ANDA was filed."[5] Upon review of the ANDA, we have determined that there were changes in the requirements for approval for chemistry after Ranbaxy filed its application. Namely, while Ranbaxy's application was under review, a USP monograph for the drug substance became official, with which Ranbaxy had to comply prior to ANDA approval (or tentative approval).

Chemistry

On May 1, 2007, approximately two months prior to the 30-month forfeiture date, a new USP monograph for the drug substance, Valsartan, became official. In response, Ranbaxy submitted a chemistry amendment on June 26, 2007, two days before the 30-month forfeiture date, to revise its drug substance specifications and test methods to comply with the monograph.[6] Specifically, Ranbaxy proposed the following changes to its drug substance specifications and test methods:

Changes in drug substance specifications:

- Requirement for identification test by IR test redefined to include USP reference standard
- Limits and requirements for Absorbance test revised as per USP monograph
- Changes in related compounds in line with USP monograph

[5] Letter to Ranbaxy Inc. fr. G. Buehler, Dir., Office of Generic Drugs (OGD), at 1 (Oct. 25, 2007).
[6] Letter to OGD fr. S. Russell, Sr. Regulatory Affairs Associate, Ranbaxy (June 26, 2007).

a. Criteria of 'Any other individual impurity' has been redefined to 'Any other individual impurity (Excluding Valsartan related compound A)'
b. Limits of (b) (4) and 'Any other individual impurity (Excluding Valsartan related compound A)' have been revised
c. Chemical name of Valsartan related compound A, Valsartan related compound B and Valsartan related compound C has been updated in line with USP 30
d. Additional note for 'In-house limits' incorporated for Valsartan related compound A and Any other individual impurity (Excluding Valsartan related compound A)

Changes in the drug substance test methods:

- Requirement for the IR test redefined and method for absorbance incorporated
- Method for 'Related Compound A' and 'Assay' updated in line with USP 30
- (b) (4)
-

Ranbaxy also provided copies of its revised drug substance specifications and test methods reflecting these changes. On July 2, 2007, FDA held a telephone conference with Ranbaxy, during which the Agency asked the firm to provide data to show equivalence between Ranbaxy's in-house test methods and the USP methods. Ranbaxy responded with a chemistry amendment on July 5, 2007.[7] The amendment was reviewed and the ANDA was tentatively approved on October 25, 2007.[8] As noted above, in the tentative approval letter, FDA stated that the USP monograph constituted a change in the requirements for approval, but the Agency did not make any determination as to whether the change caused Ranbaxy's failure to obtain tentative approval by the 30-month forfeiture date.[9]

Upon the foregoing, FDA concludes that publication of the official USP drug substance monograph for valsartan with which Ranbaxy had to comply prior to approval constituted a change in the requirements for approval. FDA further concludes that Ranbaxy's effort to comply with this new requirement, and FDA's review of that effort, was a cause of Ranbaxy's failure to obtain tentative approval by the 30-month forfeiture date. As described in detail below, FDA has considered Mylan's assertion that the publication of or changes made to a USP compendial standard cannot form the basis of a non-forfeiture decision, but concludes that Mylan's arguments are unavailing.

[7] Letter to OGD fr. U. Sankaran, Sr. Regulatory Affairs Associate, Ranbaxy (July 3, 2007).
[8] The acceptable chemistry review was not entered into DARRTS until February 5, 2008, approximately three months after the ANDA was tentatively approved.
[9] Letter to Ranbaxy Inc. fr. G. Buehler, Dir., OGD, at 1 (Oct. 25, 2007).

Labeling

FDA notes that Ranbaxy's labeling was initially determined to be acceptable on April 5, 2006.[10] On November 22, 2006, FDA approved a labeling supplement for the reference listed drug (RLD) that consisted of changes to the Warnings, Adverse Reactions, and Overdosage sections of the labeling.[11] It is unnecessary to determine whether this labeling change qualifies as an additional change in the requirements for approval that caused Ranbaxy to fail to obtain tentative approval within the 30-month timeframe, however, because, as stated above, if only one of the causes of failure to obtain tentative approval in the relevant time period was a change in or review of the requirements for approval imposed after the application was filed, an applicant does not forfeit.

Mylan's Arguments in Favor of Forfeiture

As indicated above, Mylan, as a subsequent applicant potentially blocked by Ranbaxy's exclusivity, submitted three letters to FDA asserting that Ranbaxy had failed to obtain tentative approval by the 30-month forfeiture date, and that there has been no change in or review of the requirements for approval on which an exception to forfeiture could be based. First, Mylan submitted a letter to FDA on July 24, 2012, requesting final approval of its valsartan ANDA. In this letter Mylan stated that it was unaware of any change in or review of requirements for approval that could have caused Ranbaxy's failure to obtain tentative approval by the 30-month forfeiture date. Mylan also asserted that two particular labeling changes to the RLD could not have served to delay the issuance of tentative approval to Ranbaxy.[12] Mylan then contended that to the extent that Ranbaxy had relinquished any eligibility for 180-day exclusivity under a consent decree with FDA, the Agency could not delay approval of Mylan's ANDA based on a first applicant's exclusivity period.[13]

Mylan sent a second letter to OGD on September 17, 2012, in which Mylan reiterated its assertions that Ranbaxy had forfeited and/or relinquished any eligibility for 180-day exclusivity, and that FDA should immediately approve Mylan's ANDA on September 21, 2012, the date on which a period of pediatric exclusivity preventing approval of Mylan's valsartan ANDA was due to expire.[14] To the extent FDA determined that Ranbaxy has not forfeited its eligibility for 180-day exclusivity, Mylan requested tentative approval on September 21, 2012, and the basis of the

[10] Tentative Approval Summary, Review of Professional Labeling (Apr. 5, 2006).
[11] Under the **WARNINGS/Fetal/Neonatal Morbidity and Mortality** subsection, the following was added as the third sentence of the first paragraph: "There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have taken valsartan." Under the **ADVERSE REACTIONS/Post-Marketing Experience** subsection, the following subheading and text were added: "***Blood and Lymphatic:*** There are very rare reports of thrombocytopenia." Under the **OVERDOSAGE** section, the following was added as the third sentence of the first paragraph: "Depressed level of consciousness, circulatory collapse and shock have been reported." Letter to N. Price, Novartis Pharmaceuticals Corp. fr. N. Stockbridge, FDA re. NDA 21-283/S-018 (Nov. 22, 2006).
[12] Letter to G. Geba, OGD, fr. Nitin Bhattad, at 2, note 5 (July 24, 2102).
[13] Id. at 2.
[14] Letter to G. Geba, OGD, fr. A. Miller, Mylan Pharms., at 2-3 (Sept. 17, 2012).

Agency's non-forfeiture determination.[15] On September 21, 2012, Mylan submitted a third letter to FDA, again reiterating its request and challenging FDA's conclusion, reflected in Ranbaxy's 2007 tentative approval letter, that the publication of the USP drug substance monograph for valsartan constituted a change in the requirements for approval on which a non-forfeiture decision may be based. In this third letter Mylan argues that FDA is precluded from taking the position that the publication of a USP monograph can constitute a change in or review of requirements for approval that causes a sponsor to fail to meet the 30-month forfeiture date because, Mylan asserts, FDA employees took the contrary position with regards to the approval of Mylan's ANDA for pioglitazone hydrochloride/metformin hydrochloride tablets.[16]

FDA considers Mylan's arguments in turn:

1) Mylan asserts that to the extent that Ranbaxy relinquished its eligibility for 180-day exclusivity in a consent decree, Mylan's ANDA approval cannot be withheld on the grounds of 180-day exclusivity.

Ranbaxy has not relinquished any eligibility rights related to 180-day exclusivity for valsartan tablets.[17] Mylan's assertion with regards to relinquishment therefore is inapposite.

2) Mylan asserts that no forfeiture exception may be based on changes to the RLD labeling.

As indicated above, FDA has determined that publication of the USP drug substance monograph, and Ranbaxy's resulting effort to comply with the monograph, constituted a cause of Ranbaxy's failure to obtain tentative approval by the 30-month forfeiture date. As a result, FDA expressly declined to consider whether any changes to the RLD labeling constituted an independent change in or review of requirements for approval that could have caused Ranbaxy's failure to obtain tentative approval by June 28, 2007. FDA's decision to decline to opine on this issue is consistent with FDA's interpretation of section 505(j)(5)(iv)(IV) of the Act. Under this interpretation, to determine that exclusivity has not been forfeited under section 505(j)(5)(iv)(IV), FDA must find only that acceptability of one aspect of the ANDA was delayed due to a change in or review of the requirements for approval, irrespective of other potential reasons for an applicant's failure to obtain tentative approval unrelated to a review of or change in the approval requirements. Any change to the RLD labeling therefore is not a basis on which FDA has made its non-forfeiture decision, and thus is not a basis on which Mylan can challenge that decision.

[15] Id., at 4.
[16] Letter to E. Dickinson, FDA Office of Chief Counsel, fr. W. Rakoczy, Outside Counsel for Mylan, at 2 (Sept. 21, 2012).
[17] Consent Decree of Permanent Injunction, Appendix A, at 1, *U.S. v. Ranbaxy Labs., Ltd.*, Civil Action No. .12-0250 (Jan. 26, 2012).

3) Mylan asserts that FDA is precluded from taking the position that the publication or revision of a USP monograph can constitute a change in or review of requirements for approval.

In the pioglitazone/metformin matter, Mylan was eligible for 180-day exclusivity for its ANDA for pioglitazone hydrochloride and metformin hydrochloride tablets. Mylan failed to obtain tentative approval by the 30-month forfeiture date, however, and FDA approved Mylan's ANDA without exclusivity on February 25, 2011. By letter dated February 28, 2011, Mylan requested that the Agency reconsider its prior determination that 180-day exclusivity was forfeited due to Mylan's failure to obtain tentative approval within 30 months from the date the ANDA was filed.[18] Specifically, Mylan asserted four grounds on which FDA should have concluded that Mylan had not forfeited its exclusivity:

- FDA reviewed the requirements for approval related to whether to require compliance with a new labeling template;
- FDA imposed a new approval requirement when it recommended that Mylan comply with a proposed (but not official) USP monograph for the Pioglitazone Hydrochloride drug substance;
- FDA imposed a new approval requirement by requiring compliance with a revised USP monograph for residual solvents that had become official four months after Mylan had filed its ANDA; and
- Mylan's failure to receive tentative approval by the 30-month forfeiture date was caused by FDA's delay in reviewing Mylan's ANDA, and Agency delay is not an appropriate basis on which to find an ANDA applicant has forfeited its exclusivity eligibility.

A meeting was held on May 19, 2011, between representatives from OGD, FDA's Office of Chief Counsel, and Mylan. Mylan again presented arguments as to why it believed it did not forfeit 180-day exclusivity for failure to obtain approval within 30 months.[19] Mylan then submitted a letter dated June 16, 2011, that included additional information and explanation as to why Mylan believed it had not forfeited 180-day exclusivity.[20]

Mylan's June 16 letter reiterated and expanded on its previous arguments related to the labeling template revision and the Agency's recommendation with respect to compliance with the proposed USP monograph for pioglitazone hydrochloride.[21] Mylan also offered two additional grounds on which it believed that FDA should have concluded that Mylan had not forfeited its exclusivity:

[18] Letter to OGD fr. S.W. Talton (Feb. 28, 2011).
[19] In accordance with its standard practice for this type of meeting, FDA did not take minutes.
[20] Letter to OGD fr. S.W. Talton (June 16, 2011).
[21] Id. at 10-15.

- FDA imposed a new approval requirement for Mylan's ANDA when it required a risk evaluation and mitigation strategy (REMS) and Medication Guide for the reference listed drug, and
- FDA changed the requirements for approval when it classified Mylan's addition of an alternate manufacturing site for the pioglitazone hydrochloride drug substance as a Major Amendment rather than a Minor Amendment.

Upon review of Mylan's arguments and the relevant record, FDA concluded that the addition of a Medication Guide and a REMS, together with FDA's evaluation of the effect of a change in a use code for one patent listed in the Orange Book for the RLD (a basis that Mylan did not raise), constituted changes in or review of the requirements for approval of the application imposed after the date on which the application had been filed. FDA further determined that the Agency's review of Mylan's proposed REMS and MedGuide labeling, and review of the updated patent information and evaluation of the need for a corresponding patent certification, extended past the 30-month date, and therefore was a cause of Mylan's failure to obtain tentative approval of the application by the 30-month forfeiture date.[22] In light of this conclusion, FDA expressly declined in its decisional memorandum to opine on Mylan's alternative bases for non-forfeiture including the USP issues.[23]

Mylan now argues that any decision that Ranbaxy has not forfeited exclusivity based on the publication of or change to the valsartan USP monograph would be inconsistent with oral statements made by FDA officials at the meeting with Mylan, in which FDA officials allegedly stated that changes in the USP could not constitute a change in or a review of the requirements for approval for purposes of the exclusivity forfeiture exception. First, and most importantly, in making its decision on the pioglitazone/metformin forfeiture, FDA never decided whether a change in USP requirements constituted a change in or review of requirements for approval that caused Mylan's failure to obtain a tentative approval within 30 months. Rather, as described above, FDA determined in that instance that changes in the RLD's labeling, including the addition of a Medication Guide and a REMS, and FDA's evaluation of the impact of the RLD's patent use code change on pending ANDAs, constituted changes in or a review of the requirements for approval of the application that caused Mylan's failure.[24] Although Mylan had, in that situation, asserted that both (1) a change to an existing compendial requirement, and (2) FDA's recommendation that Mylan comply with a pending proposed (but not yet official) monograph constituted changes in and/or reviews of the requirements for approval, FDA did not determine whether those changes constituted additional, independent grounds to support FDA's non-forfeiture decision. In fact, consistent with FDA's non-forfeiture determination in this instance, FDA expressly noted in the Pioglitazone/Metformin Non-forfeiture Memo that the

[22] Memorandum fr M. Shimer to ANDA No. 090406, at 6 (June 25, 2012) (Pioglitazone/Metformin Non-forfeiture Memo)
[23] Id.
[24] Id.

Agency was declining to opine on Mylan's arguments related to changes in USP monographs because the other grounds cited by Mylan provided sufficient a basis to support a conclusion of non-forfeiture.[25] FDA therefore did not, as Mylan contends, take the position in its pioglitazone/metformin forfeiture analysis that changes in proposed and/or final USP monographs could not constitute a change in approval requirements for purposes of the forfeiture exception. Instead, FDA declined to reach that issue because analysis of the effect of the USP changes on forfeiture was not necessary to support the conclusion of non-forfeiture in that case.

Second, FDA notes that the question of whether the official publication of or change in a USP monograph could constitute a change in or review of the requirements for approval that could cause a failure to obtain tentative approval is, like all forfeiture inquiries, a very fact-specific question. Such analysis involves a number of potential factors including, but not limited to, whether the monograph change is in a proposed or final monograph, the timing of any publication of or change in a monograph in relation to a particular 30-month forfeiture date, whether FDA requires compliance with the new/changed compendial standard, whether the Act requires compliance with the new/changed compendial standard, the consistency of the new/changed monograph with pre-existing approval requirements, and the nature and timing of the sponsor's efforts to comply with USP monographs, and/or of FDA's review of such efforts. As a result, FDA has not made (and indeed could not make) any broadly applicable determination (in a meeting with Mylan representatives or in any other forum) that the establishment of, or changes to, a USP monograph, can never be appropriate grounds on which to base a forfeiture decision.[26]

FDA's analyses of other forfeitures that involved new/changed USP monographs reflect the fact-specific nature of such analysis. For example, in considering whether (b) (4) forfeited its eligibility for 180-day exclusivity for (b) (4), FDA concluded, as it has here with valsartan, that there had been a change to the requirements for approval that resulted from changes in a related USP monograph. In that case, however, FDA concluded that (b) (4) failure to obtain tentative approval was not caused by its efforts to comply with these USP monograph changes. Specifically, in that case the sponsor had complied with those changes, and FDA had found the affected disciplines acceptable, prior to the 30-month forfeiture date. Instead, FDA concluded that (b) (4) failure was due to an unacceptable compliance status, the acceptability of which did not relate to the USP changes.[27] Notably, (b) (4), Mylan's Doxycycline Hyclate Delayed-release Tablets 150 mg ANDA was not blocked by exclusivity.[28] In the case of Ranbaxy's valsartan, FDA has similarly concluded that a change in the USP monograph constituted a change in the requirements for approval. In this case, however, FDA has also concluded that because the

[25] Id.

[26] To the extent that Mylan representatives construed a statement made by an FDA employee at a May 19, 2011, meeting discussing the pioglitazone/metformin forfeiture to be FDA's definitive statement on the role of USP monograph compliance in forfeiture analyses, such reliance is misplaced. See 21 CFR 10.85(k).

[27] (b) (4)

[28] Letter to S. Wayne Talton, Mylan Pharms. Inc. fr. R. West re. ANDA 091052 (Feb. 8, 2012).

monograph did not become final until approximately two months before the 30 month-forfeiture date and because Ranbaxy's chemistry amendment seeking to comply with those changes was pending as of that forfeiture date, Ranbaxy's efforts to comply with the new monograph were a cause of its failure to get tentative approval by the 30-month forfeiture date.

4) Mylan requests FDA provide the company a written explanation of FDA's decision that Ranbaxy has not forfeited its eligibility for 180-day exclusivity.

FDA regulations prevent the disclosure of the existence of an abbreviated application before an approval letter is sent to the applicant under 21 CFR 314.105 or tentative approval letter is sent to the applicant under 21 CFR 314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. 21 CFR 314.430(b). Even in cases like this in which Ranbaxy has been tentatively approved, no data or information in the application or abbreviated application is available for public disclosure prior to full approval. 21 CFR 314.430(d)(1). In light of this prohibition, FDA is severely restricted in what information the Agency can provide Mylan, or any other third-party, regarding the basis of the Agency's forfeiture determination on Ranbaxy's ANDA. FDA appreciates the challenge this presents to parties affected by a forfeiture analysis, but the Agency is nonetheless prohibited at this time from disclosing any additional information regarding the forfeiture decision directly to Mylan.

II. CONCLUSION

Upon consideration of relevant law and record, and the arguments that Mylan set forth in three separate letters to the Agency, FDA concludes that Ranbaxy has not forfeited its eligibility for 180-day exclusivity for Valsartan Tablets, 40 mg, 80 mg, 160 mg, and 320 mg.

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

/s/

MARTIN H Shimer
09/28/2012