



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville MD 20857

Marc Scheineson, Esq.  
Alston & Bird LLP  
601 Pennsylvania Avenue, N.W.  
North Building, 10<sup>th</sup> Floor  
Washington, D.C. 20004-2601

Re: Docket No. 2004P-0061/CP1 & AMD1

Dear Mr. Scheineson:

This letter responds to your citizen petition (Petition) dated February 10, 2004, on behalf of Jerome Stevens Pharmaceuticals, Inc. (JSP) asking the Food and Drug Administration (FDA) to (1) issue specific guidance for the submission of abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) consistent with current guidance and requirements for new drug applications (NDAs) for levothyroxine sodium products submitted under section 505(b)(2) of the Act; (2) not approve any ANDA for levothyroxine sodium that fails to conform to the standards for review established for 505(b)(2) applicants; and (3) immediately withdraw approval of the ANDA for levothyroxine sodium submitted by Mylan Pharmaceuticals, Inc. (Mylan) if it did not meet the same standard for review applicable to 505(b)(2) applicants.

This letter also responds to your amendment to your citizen petition dated March 31, 2004 (Amendment), asking FDA to withdraw approval of Mylan's ANDA because the bioequivalence study Mylan relied on for approval used as the reference product pre-approval Unithroid, which was not an appropriate reference material as interpreted by FDA. Finally, this letter responds to your supplement dated May 5, 2004 (Supplement), which did not request any specific relief.<sup>1</sup>

Because the Petition, the Supplement, and the Amendment raise different issues, they will be discussed separately in this response.

For the reasons that follow, the Petition and the Amendment are denied.

## I. THE PETITION

### A. Content of ANDAs for Levothyroxine Sodium Products

JSP objects to FDA's standards for approval of ANDAs for levothyroxine sodium tablets because the Agency does not ask ANDA applicants to submit exactly the same information submitted in section 505(b)(2) NDA applications for levothyroxine sodium tablets. Petition at 3-4. JSP argues that a 1997 *Federal Register* notice concerning

<sup>1</sup> The Supplement consisted of a declaration in support of the Petition.

levothyroxine sodium products supports its position that all NDA and ANDA applicants should submit the same information. As explained below, JSP is incorrect in arguing that the notice supports its position.

In 1997, FDA published the notice in the *Federal Register* declaring levothyroxine sodium a new drug ("new drug declaration"). 62 FR 43535, August 14, 1997. In the notice, FDA cited concerns about the potency and stability of the levothyroxine sodium products that were then marketed without approved applications. JSP relies on this *Federal Register* notice as the basis for its argument that NDAs and ANDAs for levothyroxine sodium should contain exactly the same information. Specifically, JSP quotes the following language from the notice: "Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or be of consistent potency from lot to lot." Petition at 3, quoting 62 FR 43535 at 43536.

JSP mistakenly relies on the new drug declaration in arguing that ANDA and NDA applicants must submit the same information for levothyroxine sodium products. The point of the 1997 new drug declaration was to require that levothyroxine sodium products be the subject of approved applications — not to require the identical content in NDAs and ANDAs. FDA will not approve an application for a levothyroxine sodium product unless the applicant, among other requirements, has demonstrated that its product is carefully and consistently manufactured, the product's potency is as labeled, and the product will remain stable through its assigned expiration period. Whether the application was submitted in the form of an NDA or an ANDA, FDA is equally assured of the quality of all approved levothyroxine sodium products. Because FDA will only approve a levothyroxine sodium product that meets the Agency's quality standards, there is no basis upon which to grant the relief the Petition requests.

#### **B. Bioavailability and Bioequivalence Studies for Levothyroxine Sodium Products**

JSP asserts that ANDA applicants for levothyroxine sodium products should conduct the same dosage form proportionality studies for bioequivalence testing that FDA asked NDA applicants to perform for bioavailability testing. Petition at 6-7. JSP's argument fails for the reasons given below. First, FDA only allows a minor difference in the number of dosage form proportionality studies that can be waived for ANDA and NDA applicants. Second, FDA's approach is justified by the applicable regulations and guidance. Furthermore, any difference in the number of studies between NDAs and ANDAs is justified by the additional information available to the ANDA applicant concerning the reference listed product's comparative dissolution tests.

FDA regulations require NDA applicants to measure the in vivo bioavailability of the drug product or submit information sufficient to permit FDA to waive the demonstration of in vivo bioavailability. 21 CFR 320.21(a). FDA regulations require ANDA applicants to demonstrate that the drug product to be marketed is bioequivalent to its reference listed drug or to submit information sufficient to permit FDA to waive the demonstration of in

vivo bioequivalence. 21 CFR 320.21(b). For multi-strength products, FDA regulations allow for the waiver of in vivo bioavailability and bioequivalence studies for some strengths when the formulations of the products are proportionally similar and the products meet an appropriate in vitro test (usually dissolution testing). 21 CFR 320.22(d)(2).

FDA issued a guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (General Considerations guidance) (issued in October 2000 and revised in March 2003). This guidance explains that bioavailability or bioequivalence testing can be waived for one or more lower strengths based on a showing that the formulations are proportionally similar and the products satisfy an appropriate dissolution test. General Considerations guidance at 13.

Dosage form proportionality means that the bioavailability of each tablet strength is proportional to its labeled content.<sup>2</sup> For example, two 25-microgram (mcg) tablets will have the same bioavailability as one 50-mcg tablet if the two tablet strengths are dosage form proportional. FDA regulations do not require dosage form proportionality studies of either NDA or ANDA applicants. However, applicants often perform such studies in order to obtain a waiver for one or more strengths of the requirement to measure in vivo bioavailability or demonstrate in vivo bioequivalence. Such waivers are important for levothyroxine sodium applications because there are up to 11 strengths of these products.

In December 2000, FDA issued a guidance for industry on *Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing*. The guidance recommended that sponsors of NDAs for levothyroxine sodium tablets conduct two bioavailability studies. One study was to determine the bioavailability of the drug product compared to an oral solution. The guidance recommended that this study be conducted using the highest strength of the product. The other study was to determine dosage form proportionality. Because hypothyroid patients are gradually titrated to an optimal dosage strength and there are 11 different strengths, the Agency concluded that it is important for levothyroxine sodium products to be dosage form proportional. NDA applicants were not asked to demonstrate dosage form proportionality by making every possible comparison between the 11 strengths (e.g., 2 25-mcg tablets = 1 50-mcg tablet, 2 50-mcg tablets = 1 100-mcg tablet) in which levothyroxine sodium products are marketed. Instead, NDA applicants were asked to perform in vivo bioequivalence studies that compared 600-mcg total doses prepared from high (2 300-mcg tablets), intermediate (6 100-mcg tablets), and low (12 50-mcg tablets) strength tablets. FDA then waived in vivo bioavailability studies on the remaining 8 strengths of levothyroxine sodium tablets based on dissolution tests and dosage form proportionality.

The recommendations in the General Considerations guidance apply to bioequivalence studies for levothyroxine sodium ANDAs. As is FDA's customary practice with ANDA applicants, the Agency asked Mylan (and would ask other ANDA applicants for

<sup>2</sup> The definition of proportionally similar formulations is contained in the General Considerations guidance, p. 12.

levothyroxine sodium products)<sup>3</sup> to demonstrate in vivo bioequivalence between its product and the innovator product using the highest strength of the reference listed drug. Specifically, FDA asked Mylan to compare two 300-mcg tablets of its product with two 300-mcg tablets of the innovator product. FDA then waived in vivo bioequivalence studies on 10 strengths of levothyroxine sodium tablets based on dissolution tests and dosage form proportionality.

Thus, for both NDA and ANDA applicants for levothyroxine sodium products, FDA waived the submission of in vivo bioavailability or bioequivalence information for many tablet strengths of their products. The above-cited regulations and guidances justify this approach. Additionally, there was not any difference in the type of studies requested by FDA for NDA and ANDA applicants. The only difference between the data submitted for the two types of applications was the number of dosage strengths waived: 8 dosage strengths were waived for NDA applicants, and 10 dosage strengths were waived for ANDA applicants.

Moreover, waiving bioequivalence studies for two additional dosage strengths for ANDA applicants is justified because ANDAs contain an additional piece of information not found in the NDA: comparative dissolution tests between the test and reference products. ANDA applicants for levothyroxine sodium products perform dissolution tests comparing each strength of the generic product to the same strength of the innovator product. These comparative dissolution tests at all strengths provide assurance that the correspondence seen at the highest strength product is valid for the other strengths.

JSP's challenge to Mylan's approval for its levothyroxine sodium product is particularly ill-founded because Mylan actually conducted more bioequivalence studies than the Agency recommended. In addition to comparing two 300-mcg tablets of its product to two 300-mcg tablets of the innovator product, Mylan also tested its product against the innovator by comparing four 125-mcg tablets and six 100-mcg tablets. Mylan's product demonstrated bioequivalence to the innovator product for all three comparisons.

### **C. Stability Data for NDAs and ANDAs for Levothyroxine Sodium Products**

JSP suggests that ANDA applicants for levothyroxine sodium should submit the same amount of stability data, at the same temperature and humidity conditions, that FDA asked NDA applicants to submit. Petition at 4. For the reasons given below, FDA's approach in requesting different information is justified by the applicable regulations and guidance. Thus, JSP's arguments are unpersuasive.

FDA's requirements concerning stability testing are described at 21 CFR 211.166. This regulation is part of FDA's current good manufacturing practice regulations and applies to all marketed drug products. Section 211.166(b) provides:

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<sup>3</sup> FDA can neither confirm nor deny whether other ANDAs for levothyroxine sodium tablets have been submitted to the Agency.

An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

FDA regulations concerning the content and format of NDAs and ANDAs do not require that a particular amount of stability data be included when an application is submitted. Section 314.50(d)(1)(ii)(a) of FDA regulations simply requires NDAs to contain "such specifications . . . as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including . . . stability data with proposed expiration dating." Section 314.94(a)(9)(i), in referencing § 314.50(d)(1), also requires that ANDA applicants submit stability information.

The fact that FDA regulations do not require applications to contain a specific amount of stability data when they are submitted or approved is based on the purpose of stability testing. Stability testing is used to assign an expiration date and also to determine the appropriate storage conditions for a drug product. A basic principle of stability testing is that testing under extremes of temperature and humidity (i.e., accelerated stability testing) can be used to assign a tentative expiration date until room temperature stability testing for the full expiration period requested has been conducted. Manufacturers are not required to demonstrate stability for a specific minimum expiration date. Instead, manufacturers can request an appropriate expiration date for a drug product based on the currently available stability data, subject to further confirmation by future stability data.

FDA generally asks NDA and ANDA applicants to submit slightly different stability information. The stability information FDA requests in an ANDA appropriately differs from that in an NDA because FDA already has evaluated information about the ANDA's reference listed drug and knows its general stability characteristics.

FDA recommends that ANDA applicants provide 3 months' accelerated and 3 months' long-term stability data for one batch of the drug product at each product strength.<sup>4</sup> FDA recommends that the accelerated stability data be generated under the same conditions recommended for NDA applicants in guidance developed by the International Conference on Harmonization (ICH). ANDA applicants customarily use ICH conditions for long-term stability data, although FDA has accepted such data using

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<sup>4</sup> The stability data to be included in an ANDA is described in the guidance, *Guideline for Submitting Documentation for the Stability for Human Drugs and Biologics (1987)* (Stability Documentation guidance).

slightly different conditions.<sup>5</sup> These data are used to set a tentative shelf life subject to the results of long-term testing.

With regard to stability data for levothyroxine sodium products in particular, FDA makes the following recommendations to NDA applicants (including 505(b)(2) applicants) in its July 2001 guidance for industry on *Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications* (Enforcement guidance):

FDA recommends that 6 months' long-term stability data and 3 months' accelerated stability data be included when the application is submitted. Primary stability data should be generated according to guidance developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Additional stability data may be submitted as an amendment during the review process, and an expiration date will be determined based on FDA review of the data submitted.

Enforcement guidance at 5.

FDA also recommends that NDA applicants for levothyroxine sodium submit three batches of stability data for each product strength before approval. For levothyroxine sodium ANDAs, the Agency recommends that applicants follow the general guidance for ANDA applicants (i.e., 3 months' accelerated and 3 months' long-term stability data for one batch of the drug product at each product strength). FDA also recommends that levothyroxine sodium ANDA applicants perform stability testing on the first three production batches produced after approval. Based on these recommendations, FDA eventually obtains a similar amount of stability data under similar conditions from both ANDA and NDA applicants for levothyroxine sodium products.

Finally, any ANDA or NDA batches that fail stability testing should be withdrawn from the market by the sponsor. A 1995 study of 800 drug product recalls by FDA's Office of Generic Drugs (OGD) found no difference in the rate of stability-related recalls between ANDA and NDA applications. The study concluded that the ANDA stability requirements provide adequate evidence to grant a tentative shelf life. Therefore, FDA has determined that the traditional stability requirements for ANDAs, although slightly different than those for NDAs, provide adequate assurance that drug products will maintain consistent quality over their lifetimes.

In support of its assertion that ANDA applicants should submit the same stability data as NDA applicants, JSP cites the Enforcement guidance. JSP suggests that the recommendations in that guidance on stability data for NDAs are also applicable to ANDAs because of the location of the recommendations in the guidance. Petition at 4.

<sup>5</sup> Prior to approval of its ANDA for levothyroxine sodium, Mylan provided 3 months' accelerated and 3 months' long-term stability data for one batch at each product strength. Mylan's stability studies were conducted at ICH conditions both for long-term data and for accelerated data.

The recommendations concerning stability data appeared after the following statement in the guidance: "A manufacturer who wishes to submit an application for [a levothyroxine sodium product] after August 14, 2001, should submit an abbreviated new drug application (ANDA)." Enforcement guidance at 4. JSP argues: "Presumably, the recommendations following this announcement in the guidance applied to 505(j) applications. FDA's silence on this issue implies that the content of ANDAs for levothyroxine products should be the same as the content of the 505(b)(2) applications for levothyroxine." Petition at 4.

The Enforcement guidance largely concerned 505(b)(2) applications and manufacturers who had submitted such applications. Any interested manufacturer would have known that the recommendations concerning stability data applied only to 505(b)(2) applications because FDA provided the same recommendations for 505(b)(2) applications in an earlier guidance for industry issued in February 2001 entitled *Levothyroxine Sodium Questions and Answers* (Q&A guidance). That guidance stated that it was "intended to assist sponsors who have questions about submitting new drug applications (NDAs) for orally administered levothyroxine sodium products." FDA simply repeated in the Enforcement guidance the recommendations about stability data for 505(b)(2) applications from the Q&A guidance.

Furthermore, the Enforcement guidance recommendation that 6 months' long-term stability data and 3 months' accelerated stability data be included with the NDA was only a *recommendation*, not a requirement, and it reflected the Agency's current thinking at the time it was issued. The NDAs for levothyroxine sodium products that have been approved contained varying amounts of stability data at the time they were submitted and at the time they were approved.

JSP also asserts that the Enforcement guidance recommendation is in conflict with other Agency guidance to ANDA applicants concerning stability data. JSP refers to FDA's August 18, 1995, Industry Letter to "All ANDA and AADA Applicants" announcing that FDA would accept for ANDAs the ICH recommendations for long-term room temperature conditions for stability studies — 25 ±2 degrees C, 60 ±5 % RH, as well as "any studies conducted at the conditions it has recommended in the past, 25-30 degrees C/ambient humidity." Petition at 4.

The portion of the letter to ANDA applicants that JSP cites does not refer to a particular amount of stability data, but only to the temperature and humidity conditions for testing. As discussed above, FDA has determined that ANDA applicants for levothyroxine sodium should submit 3 months' long-term stability data and 3 months' accelerated stability data. This approach is justified by the applicable regulations and guidance.

**D. Specific Guidance on the Content of ANDAs for Levothyroxine Sodium**

JSP asks the Agency to "issue guidance to clarify that a levothyroxine ANDA application must provide the same manufacturing data as required of 505(b)(2) applicants." Petition at 7. FDA denies JSP's request, because any additional guidance is unnecessary.

As discussed above, NDAs and ANDAs for levothyroxine sodium provide similar information. To the extent there are differences in the information provided, these differences are appropriate because an NDA must first demonstrate that the drug is safe and effective, while an ANDA then relies on FDA's finding that the reference listed drug is safe and effective.

FDA concludes that it is not necessary to issue a specific guidance concerning the content of ANDAs for levothyroxine sodium. Section 314.94 of FDA regulations describes the content and format of ANDAs generally. The content of ANDAs in the two areas JSP raises concerns about — stability and bioequivalence — are described in guidance documents. The stability data to be included in ANDAs are described in the Stability Documentation guidance. The bioequivalence requirements for ANDAs are described in the General Considerations guidance. In addition, OGD routinely communicates with potential applicants by letter responses to questions and not by the issuance of guidance documents.

Furthermore, to the extent that OGD issued drug-specific guidances in the past, these guidances usually concerned bioequivalence. The practice of issuing drug-specific bioequivalence guidances has generally ceased. On October 27, 2000, FDA published a notice in the *Federal Register* announcing the availability of the General Considerations guidance. 64 FR 64449. The notice stated that the guidance "provides general information on how to comply with the BA and bioequivalence requirements for orally administered dosage forms under the bioavailability and bioequivalence requirements regulations." The notice further stated that the guidance "is one of a set of planned core guidances designed to reduce or eliminate the need for FDA drug-specific guidances." The Agency has not issued any new drug-specific bioequivalence guidances since it made the General Considerations guidance available.

**E. Post-approval Evidence Concerning Mylan's ANDA for Levothyroxine Sodium**

JSP asserts that FDA has grounds for withdrawing approval of Mylan's ANDA for levothyroxine sodium under § 314.150 of FDA regulations because post-approval evidence indicates that the product is not safe or there is a lack of substantial evidence that the drug is effective. JSP claims that because of the need to titrate patients with levothyroxine sodium in small increments, Mylan's product cannot be presumed to be safe or effective unless dosage form proportionality studies have been conducted to demonstrate that the various strengths are dose proportional. Petition at 7-8.

As discussed above, Mylan's ANDA contained adequate information to ensure that the various strengths of its product are proportional. JSP has not submitted, and FDA is not aware of, any post-approval evidence that would constitute a basis for withdrawing approval of Mylan's ANDA.

## II. THE SUPPLEMENT

JSP submitted a supplement dated May 5, 2004, entitled "Scientific Rationale for Application of FDA Levo Guidance to Generic Drug Applicants." In the supplement, JSP states: "*In vitro* dissolution testing is needed for each strength to be marketed based on 3 production-sized batches. The intent with this requirement is to verify adequate manufacturing reproducibility." Supplement at 3.

JSP also notes in its petition that the firm's NDA contained dissolution data from multiple batches of each strength of its levothyroxine sodium product. Petition at 5. As JSP is aware, FDA asks ANDA applicants, including applicants for levothyroxine sodium products, to submit dissolution data from one batch of each strength to compare the dissolution of the generic drug with its reference listed drug. Thus, JSP appears to be suggesting that ANDA applicants for levothyroxine sodium should submit dissolution data on more than one batch of each strength because NDA applicants submitted dissolution data on multiple batches.<sup>6</sup>

The fact that FDA asks for different amounts of dissolution data from NDA and ANDA applicants is justified by scientific and regulatory principles. Furthermore, the applicable regulations and guidance support FDA's approach. Section 314.50(d)(1)(ii)(a) requires NDA applicants to submit information, among other things, concerning specifications relating to the dissolution rate of the product. Section 314.94(a)(9)(i), in referencing § 314.50(d)(1), also requires that ANDA applicants submit dissolution information. Dissolution testing is part of routine quality control for all batches of FDA-approved drug products. However, FDA generally recommends that a different number of batches be tested for NDAs and ANDAs before approval. FDA recommends that an NDA contain more dissolution data than an ANDA to establish the appropriate dissolution method and specification for that NDA product.

An NDA sponsor develops an appropriate dissolution method and specification based on the data collected in the development of the drug product. The NDA applicant must provide FDA with assurance of the validity of the dissolution method and specification for its product. Because there is no reference standard to which the NDA applicant can compare its drug product's dissolution, the applicant must compare the NDA product to itself. More than one batch of the product is needed for this comparison of dissolution data. If FDA approves the NDA, including the dissolution method and specification, the sponsor will typically establish this method and specification as a public standard through the United States Pharmacopeia (USP).

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<sup>6</sup> The remainder of the Supplement simply reiterates points raised in the Petition and already addressed in section I of this response.

FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* issued in August 1997 describes how the USP standard or a publicly available dissolution test for an approved NDA is then used to set the dissolution specification for an ANDA. Because the dissolution method and specification are already established for the reference listed drug, it is appropriate for ANDA applicants, including those for levothyroxine sodium products, to submit less dissolution information prior to approval than NDA applicants. When FDA reviews an ANDA, the reference listed drug's dissolution serves as an independent standard to which the generic drug product can be compared. Because of this comparison, it is not necessary for an ANDA to contain dissolution tests on multiple batches. Thus, FDA recommends that ANDAs for levothyroxine sodium contain dissolution information from one batch at each strength, rather than from multiple batches.

### III. THE AMENDMENT

JSP's Amendment asks FDA to withdraw approval of Mylan's ANDA because the bioequivalence study Mylan relied on for approval used as the reference product pre-approval Unithroid, which was not an appropriate reference material as interpreted by FDA.

#### A. Background

On March 26, 2003, JSP submitted a supplemental NDA seeking to have its levothyroxine sodium product Unithroid listed as AB-rated to Synthroid (manufactured by Abbott Laboratories) in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

In a letter dated May 13, 2003, Dr. David G. Orloff, Director, Division of Metabolic and Endocrine Drug Products, refused to file JSP's supplemental NDA because JSP used pre-approval Synthroid as the reference material in its bioequivalence study. On May 23, 2003, JSP requested a meeting and appealed the refuse-to-file decision. In a letter to JSP dated October 3, 2003, Dr. Robert Meyer, Director, Office of Drug Evaluation II, upheld the refuse-to-file decision. On January 23, 2004, Dr. John Jenkins, Director, Office of New Drugs, met with JSP officials at JSP's request to discuss the refuse-to-file decision.

The Unithroid product used in Mylan's bioequivalence studies was manufactured prior to approval of JSP's NDA for Unithroid on August 22, 2000. Unlike the Synthroid reference material used in JSP's bioequivalence study, FDA determined that the formulation of levothyroxine sodium JSP marketed before that approval was the same as the formulation approved in JSP's NDA. An FDA chemist, David Lewis, contacted JSP to ask if the two formulations were the same and was informed that they were. Because JSP marketed the same formulation of levothyroxine sodium prior to approval and after approval, FDA considered the samples of JSP's product used in Mylan's bioequivalence studies to be the appropriate reference material.

### B. Sameness of Pre- and Post-Approval Unithroid

JSP apparently seeks to cast doubt on the confirmation of "sameness" FDA received from the firm when it states: "*An unnamed contact* at JSP reportedly indicated that the formulation 'had not changed from the formulation that was marketed before approval.'" Amendment at 5 (emphasis added). However, JSP itself has asserted that the pre- and post-approval formulations of its levothyroxine sodium product were the same in promotional material directed at formularies. On December 28, 2000, JSP submitted a formulary kit for advisory comments from FDA's Division of Drug Marketing, Advertising and Communications. The formulary kit contained a letter stating: "The manufacturer of Unithroid has been producing the identical formulation for more than 10 years, with a record of more than 1 billion tablets produced without a recall." Therefore, JSP has no basis for suggesting that FDA improperly relied on the statement of a company official that the pre-approval formulation of Unithroid was the same as the post-approval formulation.

### C. Reference Material in JSP's Bioequivalence Study

JSP argues that "FDA has consistently taken the position that the 'Code of Federal Regulations requires that the reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application.'" Amendment at 6.

That statement is inaccurate. JSP relies on a statement from Dr. Orloff's May 13, 2003, letter refusing to file JSP's supplemental NDA seeking a therapeutic equivalence rating to Synthroid because the Synthroid product used in JSP's bioequivalence study was not the subject of an approved application. The letter cited 21 CFR 320.25(e)(3), which states that the "reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety, if the new formulation . . . is intended to be comparable to or to meet any comparative labeling claims made in relation to the drug product that is the subject of an approved new drug application."

However, JSP neglects to mention that FDA later asserted that 21 CFR 320.26 was the more relevant regulatory standard. FDA said:

Although Dr. Orloff's letter cited FDA's regulation at 21 CFR 320.25, the regulation that applies more specifically to Jerome Stevens' bioequivalence study is 21 CFR 320.26, titled "Guidelines on the design of a single-dose in vivo bioavailability study or bioequivalence study." The pertinent part of that regulation is 21 CFR 320.26(a)(1), which states: "An in vivo bioavailability and bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults."

FDA determined that pre-approval Synthroid was not the "appropriate reference material" for JSP's bioequivalence study because the batch formula differed from that of the approved Synthroid product. Specifically, pre-approval Synthroid contained an overage of levothyroxine sodium at the time of release, whereas the approved Synthroid product is manufactured to target 100 percent potency at the time of release.

#### D. Pharmaceutical Equivalence of Unithroid

While JSP fails to mention the Agency's later decision and the regulation cited in that decision, JSP does acknowledge that the Agency "has also relied on a requirement that 'pharmaceutical equivalence,' in addition to bioequivalence, of two drug product must be established in order to obtain AB rating between the two drug products." Amendment at 6.

Section 320.1(c) of FDA regulations defines *pharmaceutical equivalents* as:

drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety . . . and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

To gain approval, an ANDA must show, among other things, that the generic version has the same active ingredient in the same strength and dosage form and the same labeling (with certain limited exceptions) as a listed drug (i.e., a previously approved drug product) and that it is bioequivalent to the listed drug. 21 U.S.C. 355(j)(2)(A); 355(j)(4). The scientific premise underlying the Hatch-Waxman Amendments is that drug products that are pharmaceutically equivalent and bioequivalent are, therefore, therapeutically equivalent, and may be substituted for each other.

JSP argues that pre-approval batches of Unithroid were not pharmaceutically equivalent to post-approval batches of Unithroid.<sup>7</sup> JSP's argument is difficult to summarize because it contains many unrelated points. Therefore, we quote in full the pertinent passage in the Amendment:

Second, the pre-approval batches did not contain identical amounts of the identical active drug ingredient. They are, therefore, not pharmaceutical equivalents. As FDA is well aware, levothyroxine is an unstable ingredient that varies dramatically in potency. That is why FDA initially requested NDAs for this DESI product. That is also why even the USP

<sup>7</sup> The relevant question under the regulations is whether Mylan's product is pharmaceutically equivalent to JSP's approved Unithroid. Presumably, in making this assertion about the alleged lack of pharmaceutical equivalence between its Unithroid products, JSP is also arguing that Mylan's product was not pharmaceutically equivalent to JSP's approved Unithroid product.

manufacturing specification includes a range of 97 percent to 103 percent of the active ingredient. JSP adds an overage to the 100 percent active target in manufacturing. While JSP's formulation is more stable than its competitors, each lot of the drug varies in the level of potency at time of release, and those levels decline over time. Until JSP's NDA was reviewed, and its manufacturing establishment was inspected thoroughly, FDA could not verify that a reference material used in Mylan's application was "appropriate" and "pharmaceutically equivalent" for purposes of determining bioequivalence and bioavailability.

Amendment at 6-7.<sup>8</sup>

JSP's reference to a USP range of 97 percent to 103 percent is irrelevant to its argument that pre-approval and post-approval Unithroid are not pharmaceutically equivalent. That range is not specified in the USP monograph for levothyroxine sodium tablets; instead, the range appears in the USP monograph for the drug substance levothyroxine sodium. The USP monograph for levothyroxine sodium tablets actually permits a range of 90 to 110 percent of the labeled amount of levothyroxine sodium, but this range is irrelevant also. FDA recommends that the finished levothyroxine sodium product be formulated to contain 100 percent of the labeled claim of the active ingredient when the product is released. See the Enforcement guidance, section V.E.2.

The fact that JSP uses a manufacturing overage is also irrelevant to the argument of lack of pharmaceutical equivalence. Using an overage of the bulk drug substance is sometimes necessary because some of that substance is lost in the manufacturing process. Using a manufacturing overage does not mean that the finished drug product itself will contain an overage (i.e., contain a stability overage). Furthermore, JSP is not claiming that its pre-approval and post-approval Unithroid products differ in the amount of overage at manufacturing or release. In fact, as noted above, JSP confirmed to FDA that the Unithroid formulation did not change.

JSP's statement that "each lot of the drug varies in the level of potency at time of release" (Amendment at 6) is also irrelevant. The USP permits a range of 90 to 110 percent of the labeled amount of active ingredient for most drug products. Although FDA recommends that levothyroxine sodium products contain 100 percent of their labeled claim of active ingredient at the time of release, the USP range accounts for the natural fluctuations in the potency of drug products resulting from the numerous complexities involved in pharmaceutical manufacturing. These variations in potency are considered a natural part of the manufacturing process, including that for levothyroxine sodium products. Thus, the fact that two products may differ somewhat in potency does not render them pharmaceutically inequivalent. In fact, FDA's regulatory definition of pharmaceutical equivalents contemplates such variations in potency when it states that the two drug products "*meet the identical compendial or other applicable standard of identity,*

<sup>8</sup> Levothyroxine sodium was not reviewed in the Drug Efficacy Study Implementation (DESI) program. Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug.

strength, quality, and purity, including potency . . .” 21 CFR 320.1(c) (emphasis added). The USP range of 90 to 110 percent is the compendial standard for levothyroxine sodium tablets. Furthermore, to the extent there is a range of variation in the amount of active ingredient in levothyroxine sodium products, the permitted range is no different for an innovator product than for a generic product.

JSP also argues: “Until JSP’s NDA was reviewed, and its manufacturing establishment was inspected thoroughly, FDA could not verify that a reference material used in Mylan’s application was ‘appropriate’ and ‘pharmaceutically equivalent’ for purposes of determining bioequivalence and bioavailability.” Amendment at 6-7. This statement does not support the relief JSP requests. In connection with its NDA for Unithroid, JSP’s manufacturing facility was inspected from January 13 through 27, 2000. FDA approved the NDA for Unithroid on August 22, 2000. Mylan conducted its bioequivalence study from October 6, 2000, through November 20, 2000. Thus, at the time Mylan conducted its bioequivalence study and FDA subsequently reviewed Mylan’s ANDA, FDA had already inspected JSP’s facility and approved JSP’s NDA. In reviewing Mylan’s ANDA, FDA verified that the Unithroid product used by Mylan in its bioequivalence study was the appropriate reference material, because JSP confirmed to FDA that the Unithroid formulation inspected and approved by FDA was the same as the pre-approved Unithroid product.

#### E. Consistency of FDA’s Decisions

Finally, JSP argues that:

it would constitute the very definition of illegal “arbitrary action” by FDA to continue to honor Mylan’s ANDA approval based on pre-approval Unithroid, but refuse to file JSP’s application based on a pre-approval sample of Synthroid. It is not sufficient to differentiate Synthroid from Unithroid . . . by arguing that pre-approval lots of Synthroid may have contained a greater overage in the active ingredient. The scientific truth is that all levothyroxine degrades and that as long as the samples tested approximate the potency of the reference drug, the respective products cannot be distinguished based on overage.

Amendment at 7.

The Agency appropriately distinguished pre-approval Synthroid from pre-approval Unithroid because pre-approval Synthroid contained a stability overage while pre-approval Unithroid did not. The “Memorandum of Meeting Minutes” from the Agency’s January 23, 2004, meeting with JSP (which JSP included as an attachment to the Amendment) states (at p. 3):

The Agency noted that the sponsor [JSP] was using the fact that levothyroxine degrades over time as a substitute for using pharmaceutically equivalent products in the bioequivalence assay. The

Agency noted that stability overages are not allowed for any of the approved levothyroxine products. The Agency reiterated that formulations of new drugs are defined not simply by the list of ingredients, but also by the amount of the drug substance in the product. The Agency has concluded that because of the presence of a stability overage pre-approval and post-approval Synthroid tablets are not pharmaceutically equivalent.

Unlike pre-approval Synthroid, pre-approval Unithroid did not contain a stability overage. Thus, FDA has not been arbitrary in accepting pre-approval Unithroid as an appropriate reference material while refusing to accept pre-approval Synthroid as an appropriate reference material.

#### F. Withdrawing Approval of Mylan's ANDA

One of the listed grounds for withdrawal of approval of an NDA or ANDA is that "the applicant has failed to submit bioavailability or bioequivalence data required under part 320 of this chapter." 21 CFR 314.150(b)(5). JSP states that FDA has interpreted §§ 320.25 and 320.26 of FDA regulations to require that the reference material for a bioequivalence study be taken from a post-approval batch of Unithroid. Amendment at 6-7. JSP argues that FDA must withdraw approval of Mylan's ANDA for levothyroxine sodium because the Unithroid used in Mylan's bioequivalence studies did not come from post-approval batches of Unithroid.

As discussed above, FDA appropriately concluded that the Unithroid used in Mylan's bioequivalence studies was an appropriate reference material under FDA regulations. Therefore, this argument for withdrawing approval of Mylan's ANDA fails.<sup>9</sup>

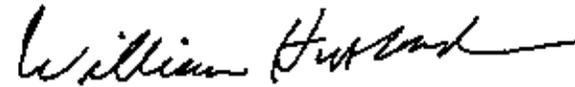
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<sup>9</sup> JSP also states that the "procedure used to notify Mylan of FDA's decision in this matter is included in § 314.151" of FDA regulations. Amendment at 7. This statement is wrong. Section 314.150(b) specifies the procedure to be used when the Agency proposes to withdraw approval for one of the reasons contained in that section. Section 314.151 applies to wholly different circumstances (i.e., when FDA has withdrawn approval of the approved drug that was the reference listed drug for an ANDA). Thus, § 314.151 has no relevance to JSP's argument.

**IV. CONCLUSION**

For the reasons discussed above, JSP has failed to provide any evidence or arguments that justify the relief it requests. Accordingly, the Petition and the Amendment are denied.

Sincerely yours,



William K. Hubbard  
Associate Commissioner  
for Policy and Planning