DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

FEB 9 2015

Laura Grablutz
Senior Director, Regulatory Affairs
Auxilium Pharmaceuticals, Inc.
640 Lee Road
Chesterbrook, PA 19087

Re: Docket No. FDA-2013-P-0371

Dear Ms. Grablutz:

This letter responds to the requests in the citizen petition dated March 26, 2013 (Petition), submitted by Auxilium Pharmaceuticals, Inc. (Auxilium). In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take certain actions regarding Vogelxo (testosterone) gel, which is the subject of new drug application (NDA) 204399,[1] held by Upsher-Smith Laboratories, Inc. (USL). The NDA for Vogelxo was approved by FDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)) and relies on Testim (testosterone gel) (NDA 021454) as a listed drug. Auxilium requests that FDA:

1. Refrain from designating Vogelxo as therapeutically equivalent (i.e., A rated) to Testim, unless:

   a. USL's skin transfer studies, hand-washing studies, skin irritation and sensitization studies, and (if required) showering studies show that Vogelxo has the same safety and effectiveness profiles as Testim;

   b. Vogelxo has the same labeling as Testim in all material aspects, including, for example, content on showering studies, interpersonal transfer studies, skin irritation and sensitization; and

   c. USL demonstrates that Vogelxo is bioequivalent to Testim;

2. Require that the labeling of Vogelxo state that the product is not interchangeable with other testosterone transdermal gel products; and

3. For the reasons set forth in the citizen petition submitted on behalf of AbbVie, Inc. in Docket No. FDA-2011-P-0610,[2] refrain from issuing a therapeutic equivalence (TE)

[1] The NDA for Vogelxo received final approval by FDA on June 4, 2014, after the submission of Auxilium's Petition. Therefore, where the Petition refers to the "proposed product," this response letter refers to Vogelxo, which is the trade name of the product for which Upsher-Smith Laboratories, Inc. (USL) holds the approved NDA.
[2] Docket No. FDA-2011-P-0610, including AbbVie's citizen petition, is available at http://www.regulations.gov/#!docketDetail;D=FDA-2011-P-0610.

rating to Vogelxo and to any other drugs described in section 505(b)(2) applications referencing Testim until the Agency conducts notice-and-comment rulemaking to establish procedures and standards for these ratings.

FDA has carefully considered the Petition; USL's comment dated February 14, 2014; Auxilium's comment dated April 10, 2014; and other information available to us. For the reasons set forth below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) abbreviated new drug applications (ANDAs).

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(l) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug is safe and effective. For a 505(b)(1) NDA, these investigations of safety and effectiveness must be conducted by or for the applicant or must be investigations for which the applicant has a right of reference.

A 505(b)(1) NDA must also include:

- a full list of the articles used as components of such drug;
- a full statement of the composition of such drug;
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
- samples of the drug as necessary;
- proposed labeling for the drug; and
- pediatric assessments.[3]

FDA approves a 505(b)(1) NDA if we find the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.[4]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Approval Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the Hatch-Waxman Amendments) created section 505(b)(2) and 505(j) of the FD&C Act, both of which are abbreviated approval pathways. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a

[3] See section 505(b)(1) of the FD&C Act.
[4] See e.g., sections 505(b)(1), 505(c) and 505(d) of the FD&C Act; and 21 CFR part 314.

generic drug approval procedure" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[5]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act. While both section 505(b)(1) and 505(b)(2) of the FD&C Act require that an application contain full reports of investigations of safety and effectiveness, in a 505(b)(2) NDA, some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[6] For instance, a 505(b)(2) NDA may reference, in support of the safety and/or effectiveness of the proposed product, published literature and/or the Agency's findings of safety and/or effectiveness for a listed drug.[7,8] Reliance on such literature or findings must be scientifically appropriate.

In some instances, a 505(b)(2) NDA may describe a drug product with substantial differences from a listed drug, including a new indication or a different active ingredient, dosage form, strength, formulation, or route of administration. However, in other instances, a 505(b)(2) NDA may describe a drug product that is essentially a *duplicate*[9] of a listed drug, but which cannot be submitted pursuant to section 505(j) of the FD&C Act because, for example, the type(s) of studies needed to support the differences between the proposed product and the listed drug (*e.g.*, differences in certain inactive ingredients) are outside the scope of what can be appropriately reviewed through the 505(j) pathway. Regardless, a 505(b)(2) NDA must support any differences from a listed drug with appropriate safety and effectiveness information and meet the same statutory standard for safety and effectiveness as a 505(b)(1) NDA.[10]

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[5] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[6] Specifically, section 505(b)(2) of the FD&C Act provides: "An application [may be] submitted under [section 505(b)(1)] for which the [safety and effectiveness] investigations . . . relied upon by the applicant [to support] approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . ."

[7] See 21 CFR 314.3 (*listed drug* means "a new drug product that has an effective approval under section 505(c) of the [FD&C Act] for safety and effectiveness or under section 505(j) of the [FD&C Act], which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the [FD&C Act], and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.").

[8] See 21 CFR 314.54; and FDA draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999) (*505(b)(2) Guidance*), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[9] See Woodcock Response Letter, Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 (October 14, 2003) (505(b)(2) Response Letter) (stating that the term *duplicate* refers to an application submitted under section 505(j) describing a product that is the same as the listed drug with respect to active ingredient, dosage form, route of administration, strength, and conditions of use, among other characteristics).

[10] See, e.g., sections 505(b)(1), 505(b)(2), 505(c), and 505(d) of the FD&C Act; see also 21 CFR 314.54; *505(b)(2) Guidance*; 505(b)(2) Response Letter for a comprehensive discussion of FDA's approach to the 505(b)(2) approval pathway.

An ANDA applicant relies on the Agency's finding of safety and effectiveness for the reference listed drug (RLD)[11] and does not submit the same types of clinical investigations to demonstrate safety and effectiveness needed for approval of a 505(b)(1) NDA. Rather, section 505(j) of the FD&C Act generally requires that an application for a duplicate of the RLD demonstrate that it is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling.[12] An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD.[13] FDA must approve the ANDA unless we find that there is insufficient evidence of the foregoing or there is inadequate information to ensure the identity, strength, quality, and purity of the drug.[14]

B. Bioavailability and Bioequivalence

A demonstration of bioequivalence (BE) is statutorily required for an ANDA. Although bioequivalence and bioavailability studies are not statutorily required for every NDA, such studies can be integral to showing an NDA meets the statutory requirement of safety and effectiveness, *e.g.*, during the investigational phase of drug development, post-approval changes to approved drug products (NDA supplements), or, as relevant here, approval of 505(b)(2) NDAs.[15]

In particular, if a 505(b)(2) NDA applicant relies upon the Agency's previous finding of safety and/or effectiveness for a listed drug (e.g., as USL relied on Testim), then a scientific bridge to the listed drug is needed. This scientific bridge often includes a bioequivalence or bioavailability study comparing the systemic exposures of the proposed product with those of the listed drug. An acceptable scientific bridge enables the applicant to rely on the Agency's previous finding of safety and/or effectiveness for the listed drug.[16]

Bioavailability studies measure "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action."[17] Bioavailability data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug.[18]

Bioequivalence studies measure the release, and subsequent absorption into systemic circulation, of a drug substance in the proposed product in comparison to the RLD. A drug product will be determined to be bioequivalent to the RLD if "the rate and extent of absorption of the drug do

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[11] See 21 CFR 314.3(b) (*reference listed drug* means "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its [ANDA].").
[12] See, e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act; *see also* 21 CFR 314.94.
[13] See, e.g., sections 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act.
[14] See, e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act; *see also* 21 CFR 314.94.
[15] *See e.g.*, FDA draft guidance for industry *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations* (March 2014) (*BA/BE NDA/IND Guidance*), at 3 available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; *505(b)(2) Guidance*, at 8-9.
[16] *See 505(b)(2) Guidance*, at 8-9.
[17] *See* section 505(j)(8)(A)(i) of the FD&C Act; *see also* 21 CFR 320.1(a).
[18] *See e.g.*, *BA/BE NDA/IND Guidance*, at 3.

not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient…."[19]

FDA regulations in part 320 (21 CFR part 320) establish acceptable methodologies for determining the bioavailability and bioequivalence of drug products.[20] While both types of studies measure the release of a drug substance from a drug product and subsequent absorption into systemic circulation, demonstrating bioequivalence involves a more formal comparative test that uses specific references with specified criteria for comparisons and predetermined limits for such criteria.[21]

Specifically, FDA generally recommends, for bioequivalence studies, administration of single doses of the test and reference drug products to subjects during the respective treatment phases, with measurement of the plasma concentrations of the test and reference drugs over time.[22] The relevant pharmacokinetic (PK) parameters calculated from these data include the area under the plasma concentration *curve vs. time* (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the *extent* of absorption (*i.e.*, how much of the drug in the given dose was absorbed). The other relevant PK parameters are the maximum or *peak* drug concentration (C_{max}) and the time required to reach the peak drug concentration after administration (T_{max}), which reflect the rate of absorption.[23] FDA considers products bioequivalent when the 90 percent confidence intervals (CIs) for test/reference AUC and C_{max} parameter ratios are within an 80 to 125 percent acceptance interval.[24]

C. TE Evaluations

Drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents[25] and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[26] FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain

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[19] *See* section 505(j)(8)(B)(i) of the FD&C Act; 21 CFR 320.1(e); 21 CFR 320.23(b).

[20] Courts have expressly upheld FDA's implementation of these regulations. *See e.g.*, *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995) and *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

[21] *See e.g.*, *BA/BE NDA/IND Guidance*, at 4.

[22] *See* Orange Book Preface at viii-ix; FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; *see also* the FDA guidance for industry *Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations* (March 2003) available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Although the guidance primarily addresses orally administered drug products, it is also generally applicable to non-orally administered drug products where reliance on systemic exposure measures is suitable to document bioavailability and bioequivalence (*e.g.*, transdermal delivery systems and certain rectal and nasal drug products); *BA/BE NDA/IND Guidance*.

[23] Id.

[24] *See e.g.*, FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence* (January 2001) available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[25] *See* 21 CFR 320.1(c) (defining pharmaceutical equivalents); *see also* Orange Book Preface at vi-vii.

[26] *See* Orange Book Preface at vii.

identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice (CGMP) regulations.[27] In 1979-1980, FDA first published in the Federal Register these criteria for TE evaluations (or ratings) in the context of a notice-and-comment rulemaking amending FDA disclosure regulations.[28]

The 1979-1980 notice-and-comment rulemaking put sponsors and the public on notice that FDA will make TE ratings publicly available using the above criteria. TE evaluations are listed by FDA in the Orange Book for "multisource" prescription drug products approved under section 505 of the FD&C Act, including products approved pursuant to 505(b)(2) NDAs and ANDAs.[29] Drug products are assigned an "A" as the first letter of their TE rating if they are products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. Drug products are assigned a "B" as the first letter of their TE rating if they are products that at this time FDA considers not to be therapeutically equivalent to other pharmaceutically equivalent products.[30] Drug products also are assigned a second letter as part of their TE rating which provides additional information on the basis of FDA's evaluations.[31] The Orange Book Preface also sets forth the history of TE evaluations (including the publication of TE criteria in the context of the 1979-1980 notice-and-comment rulemaking), legal status, and general policies.[32]

D. Testim and Vogelxo

On October 31, 2002, FDA approved NDA 021454 for Testim (testosterone gel), held by Auxilium. Testim is indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).[33] Testim is approved for topical application to the shoulders and/or upper arms.[34]

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[27] Id.

[28] *See* 21 CFR 20.117; *see also* 44 FR 2932 (Jan. 12, 1979); 45 FR 72582 (October 31, 1980) (adding paragraph (a)(3) to 21 CFR 20.117 which states, in relevant part, that FDA will make publicly available certain new drug information, including a listing that includes "for each active ingredient in a particular dosage form for which there is more than one approved application, an evaluation of the [TE] of the drug products covered by such applications.").

[29] *See* Orange Book Preface at iv, xi (stating that the term "multisource" generally is used to describe pharmaceutically equivalent drug products that are available from more than one manufacturer). We also note that the term "multisource" was used in the preambles to the 1979-1980 notice-and-comment rulemaking, before the enactment of the Hatch-Waxman amendments creating the 505(j) and 505(b)(2) approval pathways. *See* 44 FR 2932; 45 FR 72582. We generally do not repeat the term "multisource" in connection with TE evaluations or 505(b)(2) NDAs for ease of reference in this response.

[30] *See* Orange Book Preface at xiii-xx.

[31] Id.

[32] *See e.g.*, Orange Book Preface at iv-v, xi; *see also* 44 FR 2932; 45 FR 72582.

[33] See Currently Approved Product Labeling for Testim (June 19, 2014).

[34] Id.

On June 4, 2014, FDA approved NDA 204399 for Vogelxo (testosterone) gel under section 505(b)(2) of the FD&C Act. The Vogelxo NDA included, among other things, studies supporting effectiveness (a pivotal comparative bioavailability study) and safety (e.g., transfer potential studies) and relied, in part, on FDA's findings of safety and effectiveness for the listed drug, Testim.[35] Like Testim, Vogelxo is approved for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).[36] Also, like Testim, Vogelxo is approved for topical application to the shoulders and/or upper arms.[37] Vogelxo also shares the following characteristics in common with Testim: the same active ingredient (testosterone), dosage form (gel), route of administration (transdermal), and strength (50 mg of testosterone in 5 g of gel).[38,39] Vogelxo and Testim differ in that they use certain different inactive ingredients (e.g., different penetration enhancers).

E. Risk of Secondary Transfer (Transfer Potential)[40]

Testosterone is the active ingredient in Testim and Vogelxo. The skin serves as a reservoir for the sustained release of testosterone into systemic circulation. Approximately 10 percent of the testosterone applied on the skin surface is absorbed into the systemic circulation during a 24-hour period.[41] Approximately 90 percent remains on the skin surface.

In 2009, FDA became aware of cases of secondary exposure of women and children to topical testosterone gel products caused by inadvertent drug transfer from adult males using the products (risk of secondary transfer). The risk of secondary transfer associated with testosterone gel products has been reported to cause virilization in women and children, some of which is irreversible. Signs and symptoms of secondary exposure have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age.[42] This risk of secondary transfer is a function of both the amount of residual product that remains on the skin of the patient after application and the amount and rate of absorption of the product in a person who comes in contact with the patient being treated with

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[35] See, e.g., Vogelxo Deputy Director for Safety Summary Review (Aug. 15, 2013) (Vogelxo DDS Summary Review).

[36] See Currently Approved Product Labeling for Vogelxo (June 4, 2014).

[37] Id.

[38] Id.

[39] We note that Vogelxo is also available in a metered dose pump supplying 60 doses of 12.5 mg testosterone per dose.

[40] This section summarizes the Agency's understanding regarding risk of secondary transfer for topical testosterone gel products as set forth in two other citizen petition responses: Woodcock Response Letter, Docket No. FDA-2009-P-0123 (August 26, 2009) (Testim Response Letter) and Woodcock Response Letter, Docket No. FDA-2010-P-0196 (October 4, 2010) (Perrigo Response Letter). The Testim Response Letter and Perrigo Response Letter are the sources of the text in this section unless otherwise noted.

[41] See also Currently Approved Product Labeling for Testim (June 19, 2014) and Currently Approved Product Labeling for Vogelxo (June 4, 2014).

[42] FDA addressed these risks in April 2009 by requiring safety-related labeling changes, including requiring a boxed warning cautioning about secondary exposure to testosterone and a Medication Guide (a form of FDA-approved patient labeling) discussing these risks.

the product. However, proper application of the topical testosterone gel products, along with use of a clothing barrier, can reduce the risk of secondary transfer to acceptable limits.[43]

In light of this information, FDA determined, in the context of ANDAs for topical testosterone gel products, that some differences in inactive ingredients, including, but not limited to, differences in penetration enhancers, trigger the need for a study to evaluate the risk of secondary transfer (or transfer potential study), as well as a hand-washing study to determine whether hand-washing affects the amount of residual product on the skin.[44] FDA therefore concluded that any application submitted for a proposed topical testosterone gel product that uses a different penetration enhancer than the RLD uses must include transfer potential and hand-washing studies. Because such studies are safety studies that go beyond what FDA will review in an ANDA, the practical effect of this determination is that such an application will be submitted as an NDA under section 505(b) of the FD&C Act, rather than an ANDA under section 505(j) of the FD&C Act.

In 2009, USL, which had originally submitted an ANDA for a proposed topical testosterone gel product with different inactive ingredients from the RLD, received a letter from FDA's Office of Generic Drugs (OGD) regarding the use of the different inactive ingredients and risk of secondary transfer of testosterone.[45,46] Accordingly, USL resubmitted its application as a 505(b)(2) NDA and included appropriate studies and information consistent with the Agency's determination and applicable standards for approval.

II. DISCUSSION

A. TE Rating for Vogelxo

Your Petition (at 1) requests that FDA refrain from assigning an A rating to Vogelxo, indicating that the product is therapeutically equivalent to Testim unless: (1) USL's skin transfer studies, hand-washing studies, skin irritation and sensitization studies, and (if required) showering studies, show that the proposed product has the same safety and effectiveness profile as Testim; (2) Vogelxo has the same labeling as Testim in all material aspects, including, for example, content on showering studies, interpersonal transfer studies, skin irritation and sensitization; and

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[43] See, e.g., Mazer, N, et al., 2005, Transfer of Transdermally Applied Testosterone to Clothing: A Comparison of a Testosterone Patch Versus a Testosterone Gel, J Sex Med, 2: 227-234; de Ronde, W, 2009, Hyperandrogenism After Transfer of Topical Testosterone Gel: Case Report and Review of Published and Unpublished Studies, Hum Reprod, 24:425-8; Rolf, C, Knie, U, Lemmitz, G, and E Nieschlag, 2002, Interpersonal Testosterone Transfer After Topical Application of a Newly Developed Testosterone Gel Preparation, Clin Endocrinol, 56:637-641.

[44] While differences in inactive ingredients other than penetration enhancers may also trigger the need for transfer and hand-washing studies, your Petition addresses only penetration enhancers. Therefore, this response likewise addresses only penetration enhancers.

[45] See, e.g., Vogelxo DDS Summary Review at 3.

[46] This policy subsequently was embodied in the FDA's "Draft Guidance on Testosterone" (stating that OGD plans to receive ANDAs for duplicates of topical testosterone gel 1% only if proposed formulations are qualitatively and quantitatively the same as the RLD. OGD explained that this policy was based on "significant safety concerns pertaining to the transfer of testosterone to others and the current inability of [OGD] to adequately determine which new inactive ingredient(s) or change(s) in the formulation may significantly affect the safety of testosterone gel"), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347048.pdf.

(3) USL demonstrates that Vogelxo is bioequivalent to Testim. We address your assertions below, but, for ease of discussion, present them in a different order.

1. TE Criteria – Vogelxo

As explained in the Orange Book Preface (at vii), drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. The Orange Book Preface explains further that FDA classifies as therapeutically equivalent those products that meet the five criteria described above in section I.C. FDA has concluded that Vogelxo meets these criteria because Vogelxo is: (1) approved as safe and effective; (2) pharmaceutically equivalent to Testim in that it (a) contains an identical amount of the same active drug ingredient (testosterone) in the same dosage form (gel) and route of administration (transdermal), and (b) meets compendial or other applicable standards of strength, quality, purity, and identity; (3) bioequivalent to Testim as discussed below; (4) adequately labeled; and (5) manufactured in compliance with Current Good Manufacturing Practice (CGMP) regulations.

2. Your Assertions Regarding Same Clinical Effect (Bioequivalence) and Safety Profile

In the Petition (at 9), you state that although FDA can often infer that two products meet the standards for TE because they fulfill the Agency's basic TE criteria, this approach is sometimes inappropriate.[47] You contend that unless USL's studies demonstrate that Vogelxo has safety and effectiveness profiles equivalent to Testim, FDA should not designate Vogelxo as therapeutically equivalent to Testim. You state that Vogelxo uses different inactive ingredients than Testim, including different penetration enhancers, and assert that USL must therefore show, through appropriate studies, that Vogelxo will have the same safety and effectiveness profiles as Testim for it to be considered therapeutically equivalent.

a. Bioequivalence – Comparative bioavailability study (Study P06-011)

In your Petition (at 12), you state that if Vogelxo is not bioequivalent to Testim, FDA cannot rate it as therapeutically equivalent to Testim. You state that an A rating under those circumstances would be inconsistent with FDA's TE criteria and would be unsafe. As explained above, FDA

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[47] You cite as an example of therapeutic inequivalence oral contraceptives packaged in 21-day packages without placebos and those packaged in 28-day packages with 7 placebos; and you refer to the Agency's statements in the Woodcock Response Letter, Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040 (July 29, 2009) at 4. The Agency stated:

> Where products with the same active ingredient, strength, dosage form, and route of administration have differences in packaging configurations, inactive ingredients, or other differences that have significant therapeutic implications or otherwise require additional clinical studies to establish safety and effectiveness[,]...the products will not meet the standards for ANDA approval. In *some* such cases, bioequivalent and pharmaceutically equivalent products have not been considered therapeutic equivalents. . . ." (emphasis added).

Although the additional clinical studies required to establish safety for Vogelxo precluded approval as an ANDA, they do not preclude a finding that Vogelxo is therapeutically equivalent to Testim as discussed in the text.

classifies as therapeutically equivalent products that are bioequivalent and meet the other specified criteria.

To support approval of Vogelxo, USL conducted, among other studies, an open-label, randomized, 2-treatment, 4-way replicate crossover comparative bioavailability study (Study P06-011) under fasting conditions that compared equal doses of Vogelxo (test product) and Testim (reference product). Each treatment consisted of a single application of a 2 x 5 gram (100 mg) of Vogelxo or Testim applied over a 500 cm^2 area on the upper arms/shoulder/back. A series of blood samples were collected before and after dosing to measure testosterone concentration.[48] The C_{max} results satisfied the criteria for BE[49] with a 90 percent CI of 96.9 to 111.18 percent. The AUC results satisfied the criteria for BE with a 90 percent CI of 104.55 to 116.61 percent for 0 to 24 hours and 104.19 to 117.49 percent for 0 to 72 hours.[50] FDA determined that the results were adequate to demonstrate BE between Vogelxo and Testim.[51] FDA concluded that Vogelxo meets this and the other criteria for TE as discussed elsewhere in this response. Accordingly, Vogelxo can be expected to have the same clinical effect as Testim when used as specified in the approved labeling.[52]

It is important to note that the Agency's concerns regarding use of different penetration enhancers in topical testosterone gel formulations are related to safety, not clinical efficacy. The potential of different penetration enhancers to impact efficacy is directly measured in USL's comparative bioavailability study. Study P06-011 demonstrated that the differences in penetration enhancers in Vogelxo, as compared to Testim, do not result in significantly different release of the drug from the formulations. Therefore, despite use of certain different inactive ingredients, Vogelxo can be expected to have the same clinical effect as Testim when used as specified in the labeling.

b. Additional studies

In your Petition (at 1), you request that FDA refrain from assigning an A rating to Vogelxo, indicating that the product is therapeutically equivalent to Testim unless, among other things, USL's skin transfer studies, hand-washing studies, skin irritation and sensitization studies, and (if required) showering studies, show that the proposed product has the same safety and effectiveness profile as Testim. As discussed above in section I.E, an application submitted for a proposed topical testosterone gel product that uses a different penetration enhancer than the one used by the RLD must include additional studies to establish formulation-specific acceptability.

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[48] See Vogelxo Clinical Pharmacology Review (July 12, 2013) (Vogelxo Clinical Pharmacology Review) at 6-8.
[49] See section I.B above for a discussion of BE.
[50] See Vogelxo Clinical Pharmacology Review at 6-8.
[51] Id.
[52] It is well-established that sponsors of 505(b)(2) NDAs may rely on the Agency's previous findings of safety and/or effectiveness for a listed drug, in this case Testim, to support the safe and/or effective use of their products, to the extent it is scientifically appropriate to do so, as is the case here. Because Vogelxo shares characteristics in common with Testim, such as same active ingredient, dosage form, strength, route of administrations, and the products were adequately bridged to Testim through the pivotal comparable bioequivalence study, it is scientifically appropriate to rely on the Agency's findings of efficacy for the listed drug, Testim, to support the conclusion that Vogelxo is effective when applied to the shoulders and/or upper arms.

As described below, for Vogelxo, formulation-specific acceptability was demonstrated in the skin irritation-sensitization, transfer, and hand-washing studies that were submitted in the NDA.[53,54]

i. USL's irritation and sensitization study (Study P08-001)

USL's irritation and sensitization study (Study P08-001) was a single-center, within-subject, randomized, double-blind study with 255 healthy adult male subjects that evaluated the cumulative irritation and sensitization produced by Vogelxo compared with Testim.[55] Each subject received all 4 test materials (i.e., Vogelxo, Testim, positive irritant control, and low irritant control). Study P08-001 evaluated the skin irritation response during the 21-day induction phase using the Berger/Bowman Skin Irritation Scale.[56] The induction phase was followed by a 2-week rest phase, after which the subjects were challenged (i.e., dosed) and evaluated for sensitization. Subjects with reactions suggestive of sensitization were re-challenged 3 to 4 weeks after resolution of the original reactions. Assay sensitivity was established with the observation of expected skin reactions using the positive irritant control and the low irritant control. The actual irritation/sensitization score was a combination of a numerical and letter score. Letter scores were converted into numerical equivalents.

Statistical analysis of the data comparing the converted cumulative irritation evaluation scores indicated that Vogelxo is no more irritating than Testim when topically applied over a continuous 21-day period.[57] FDA concluded that the irritation potential of Vogelxo is similar to that of Testim.[58] With respect to sensitization, there were no statistical evaluations; only the number of reactions observed and severity of them were reported. Results from the sensitization data for all subjects indicated that both Vogelxo and Testim demonstrate a low, but similar, propensity for inducing sensitization (i.e., allergic contact dermatitis).[59] FDA concluded, based on the results of the challenge and re-challenge phase of the study, that the sensitization potential of Vogelxo is similar to that of Testim.[60]

ii. USL's transfer study (Study P10-003)

USL's transfer study (Study P10-003) was a single-center, randomized, open-label, 3-way crossover study involving 48 male-female couples that assessed the interpersonal transfer potential of its product with and without using a clothing barrier or after washing the application site.[61] In Study P10-003, one 5 g tube of the test product was applied topically over a 500 cm^2

[53] See, e.g., Vogelxo DDS Summary Review at 8.
[54] In general, showering studies for 505(b)(2) NDAs for transdermal testosterone gel products are needed only under certain circumstances not applicable here. See generally Woodcock Response Letter, Docket FDA-2010-P-0196 (Oct. 4, 2010).
[55] See Vogelxo Clinical Review (Aug. 12, 2013) at 25-32.
[56] Id.; see also Berger, RS and JP Bowman, 1982, A Reappraisal of the 21-Day Cumulative Irritation Test in Man, J Toxicol – Cutan Ocul Toxicol, 1(2):109-115.
[57] Vogelxo Clinical Review at 55.
[58] See also Vogelxo DDS Summary Review at 9 and Vogelxo Clinical Review at 57.
[59] See Vogelxo Clinical Review at 58.
[60] Id.
[61] See Vogelxo Clinical Pharmacology Review at 8-10; Vogelxo Clinical Review at 70.

area of the shoulder/upper arm of one side of the male subject's body. The male subjects then followed one of three treatments: (1) washing the application site before contact with female partners, (2) wearing clothing to cover the application site during contact, or (3) engaging in direct skin-to-skin contact with female partners without washing and without using a clothing barrier. After establishing a testosterone baseline for the female partners, testosterone levels were characterized for the female partners following contact with the male partners post-dosing.[62]

Study P10-003 demonstrated that direct skin-to-skin contact between male-female partners following dosing with Vogelxo resulted in a 277 percent increase in testosterone area under the curve (AUC) in females. In contrast, contact with a clothing barrier resulted only in a 4 percent increase in testosterone AUC, and contact after washing of the application site resulted only in a 9 percent increase in testosterone AUC. The change in baseline in testosterone serum concentration was insignificant for contact with a clothing barrier and contact after washing of the application site. From this study, FDA concluded that wearing clothing or washing the application site are two effective methods for preventing clinically significant transfer of Vogelxo (testosterone) between dosed (treated male) and non-dosed individuals (non-treated female).[63] When the application site was covered with clothing or washed before contact, the post-exposure maximum serum testosterone levels of non-dosed individuals (non-treated females) was within the normal range for healthy women.[64]

FDA does not require a comparative study between the test and reference product to evaluate the risk of secondary transfer of testosterone. The Agency's primary interest in evaluating transfer potential of testosterone is determining whether a clothing barrier or other measures provide an adequate level of protection from transfer. This, in turn, allows FDA to evaluate the safety of the product and to determine appropriate labeling for the product. Study AUX-206 and Study AUX-209 in the Testim NDA demonstrated that a clothing barrier provides adequate protection from transfer of Testim.[65] Likewise, Study P10-003 demonstrated that using a clothing barrier or application-site washing provides adequate protection from transfer of Vogelxo. Accordingly, both Testim and Vogelxo exhibit acceptable transfer properties when the products are used according to the approved labeling.

iii. USL's hand-washing study (Study P10-002)

USL's hand-washing study (Study P10-002) was a randomized, open-label, 3-way crossover study to assess the extent that hand washing removes the product from the hands.[66] In Study P10-002, subjects topically self-applied the entire contents of one 5 g tube of the test product over a 500 cm^2 area of the upper shoulder/arm opposite to the subject's dominant hand. Subjects then followed one of three treatments: (1) subjects had hand-swab samples collected immediately after applying the drug and again after washing, rinsing, and towel-drying; (2) subjects had hand-

[62] Id.
[63] Id.
[64] See Vogelxo Clinical Review at 70.
[65] See e.g., Testim Medical Review (Oct. 30, 2002) at 7 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-454_Testim_Medr.pdf.
[66] See Vogelxo Clinical Pharmacology Review at 10-12.

swab samples collected after air-drying for 3 minutes following product application and again after washing, rinsing, and towel-drying; or (3) subjects had hand-swab samples collected after air drying for 3 minutes following drug application and again after washing, rinsing, and air drying.[67]

The results of Study P10-002 demonstrated that the removal of testosterone following hand washing was similar for all treatments (99.8%, 98.7%, and 99.0% removal, respectively).[68] FDA concluded that washing hands with or without a drying period for the gel prior to washing allows nearly complete removal of Vogelxo from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.[69] Similarly, based on information submitted by Auxilium, FDA concluded that thorough washing of the palms following application of Testim removes any residual testosterone.[70]

In addition, we noted that Vogelxo and Testim are approved with substantially the same labeling with respect to *Indications and Usage*, *Contraindications*, *Warnings and Precautions*, *Adverse Reactions*, *Drug Interactions*, *Clinical Pharmacology*, *Patient Counseling Information*, among other sections. The approved labeling reflects FDA's conclusion that Vogelxo poses substantially the same risks as Testim.

In sum, based, in part, on the results of the comparative bioavailability study, FDA concluded that Vogelxo can be expected to have the same clinical effect as Testim. Based on the results of the skin irritation-sensitization study, FDA concluded that both the irritation potential and sensitization potential of Vogelxo are similar to that of Testim. And based on the results of the transfer and hand-washing studies for Vogelxo and Testim, FDA concluded that, for both products, a clothing barrier provides an adequate level of protection from testosterone transfer, and hand-washing adequately removes residual testoterone. Accordingly, when Vogelxo is used under the conditions specified in the labeling, it can be expected to have the same safety profile as Testim.

3. Your Assertions Regarding Vogelxo's Labeling

In your Petition, you state that FDA should not designate Vogelxo as therapeutically equivalent to Testim if Vogelxo's labeling differs from Testim's labeling in any significant way (Petition at 10). You assert (at 10) that the labeling of therapeutic equivalents may differ only in "minor aspects." You contend that differences in the labeling, with respect to the description of transfer, skin irritation and sensitization, or showering studies, cannot be considered "minor." You claim (at 11) that if the description of these safety studies in Vogelxo's labeling differs from the description in Testim's labeling, then "it will not be true that the products 'can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile,' as is required for therapeutic equivalents." Accordingly, you state that if

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[67] Id.
[68] Id.
[69] Id.
[70] See Testim Clinical Pharmacology and Biopharmaceutics Review (Oct. 30, 2002) at 5 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-454_Testim_BioPharmr.pdf.

Vogelxo's labeling regarding transfer, application site reactions, or showering after application differs from that of Testim's labeling, FDA should not assign an A rating to Vogelxo.

As explained in the Orange Book Preface (at vii):

> The FDA considers drug products to be therapeutically equivalent if they meet the [TE criteria], even though they may differ in certain other characteristics, such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time[,] minor aspects of labeling (e.g., the presence of specific pharmacokinetic information)[,] and storage conditions.

In the case of Vogelxo and Testim, the labeling of the products is substantially the same with respect to *Indications and Usage*, *Contraindications*, *Warnings and Precautions*, *Adverse Reactions*, *Drug Interactions*, *Clinical Pharmacology*, *Patient Counseling Information*, among other sections. In addition, both Vogelxo and Testim are approved with the same boxed warning regarding secondary exposure to testosterone and the same Medication Guide for distribution to patients. The approved product labeling for both Vogelxo and Testim appropriately reflects FDA's findings from the review of studies submitted in the NDAs. Any differences in the descriptions or results of studies, e.g., transfer potential studies for Testim and Vogelxo, are not clinically significant and are therefore considered minor differences in labeling that would not preclude an A rating.[71] Based on the TE criteria as they relate to Vogelxo, together with the analysis of your assertions, FDA has determined that Vogelxo can be substituted for Testim with the full expectation that it will produce the same clinical effect and safety profile.

B. Labeling Statement

In the Petition (at 13), you request that FDA require the labeling for Vogelxo to state that the product is not interchangeable with other topical testosterone gel products. You state that the labeling of numerous topical testosterone gel products bear statements regarding their non-interchangeability, such as the AndroGel 1% labeling, which bears the two statements below.

- "Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure." (limitation-of-use statement); and

- "The application site and dose of AndroGel 1% are not interchangeable with other topical testosterone products." (non-interchangeability statement).

[71] Your Petition notes (at 10-11) certain differences in the description of safety studies in the labeling for Perrigo's testosterone gel product compared to the labeling of AndroGel 1%. As with the differences in the labeling of Vogelxo and Testim, we do not agree that those differences are more than "minor." With respect to the transfer studies, although the Perrigo transfer study showed increases over baseline in mean total testosterone concentrations in females following secondary exposure when the application site was covered with a clothing barrier, the serum levels of testosterone, as with AndroGel 1%, remained within normal ranges for females. For both Perrigo's product and AndroGel 1%, transfer is effectively mitigated by use of a clothing barrier. The labeling of both products appropriately reflects this conclusion. See Woodcock Response Letter, Docket Nos. FDA-2011-P-0610 and FDA-2013-P-0371 (July 23, 2014).

You state (at 13) that FDA should require similar labeling statements for Vogelxo, even if FDA finds Vogelxo to be therapeutically equivalent to Testim. You further state that Vogelxo is likely to have substantial differences from other approved testosterone gel products, even if it is therapeutically equivalent to Testim. You assert (at 13) that such statements will ensure that prescribers and patients are aware of the differences and will help prevent inappropriate substitutions.

The approved labeling for Vogelxo bears the limitation-of-use statement.[72] The addition of the non-interchangeability statement to the Vogelxo labeling would be misleading because it would incorrectly suggest that Vogelxo is not interchangeable with any other topical testosterone products, including Testim. FDA has determined, as discussed above, that Vogelxo is therapeutically equivalent to Testim, and therefore, the two products are interchangeable. Accordingly, it would not be appropriate to add the non-interchangeability statement to the approved labeling for Vogelxo. Further, we have concluded, at this time, that the limitation-of-use statement by itself is appropriate and not misleading.

We note further that FDA's assessment of whether, in fact, specific topical testosterone gel products meet FDA's TE criteria and are interchangeable with each other is appropriately conveyed by the TE listings in the Orange Book, consistent with our approach to other drug products. In cases where more than one listed drug of the same active ingredient, dosage form, route of administration, and strength has been designated under the same heading in the Orange Book (e.g., Testim and AndroGel 1%), a number is added to the end of the AB code to make a three-character code (i.e., AB1, AB2, AB3, etc.).[73] The three-character code makes clear that the listed drugs that appear to be pharmaceutical equivalents have not been shown to be bioequivalent to each other and that a product that is therapeutically equivalent to one of the listed drugs (Testim) has not been shown to be therapeutically equivalent to the other (AndroGel 1%).

For the above reasons, it is not necessary or appropriate, at this time, to require that Vogelxo bear the non-interchangeability statement you request. We recognize, however, that it is possible that variation in the approved labeling for topical testosterone gel products may cause confusion. Accordingly, we intend to consider further these labeling differences in our on-going efforts to harmonize the approved labeling for drug products in the same class.

C. Notice and Comment Rulemaking

For the reasons set forth in the citizen petition submitted on behalf of AbbVie, Inc. in Docket No. FDA-2011-P-0610, you request (at 2 and 13-14) that FDA refrain from issuing a TE rating to Vogelxo and to any other drugs described in section 505(b)(2) applications referencing Testim until the Agency conducts notice-and-comment rulemaking to establish procedures and standards for these ratings. FDA previously denied this request in its July 23, 2014, response letter available in Docket Nos. FDA-2011-P-0610 and FDA-2013-P-0371. We refer you to that letter for a detailed explanation regarding the basis for the denial.

[72] See Currently Approved Product Labeling for Vogelxo (June 4, 2014).
[73] See Orange Book Preface at xv.

III. CONCLUSION

For the reasons stated above, your Petition is granted in as much as it requests that we refrain from assigning an A rating to Vogelxo unless it satisfies FDA's TE criteria with respect to Testim. As discussed above, Vogelxo satisfies the TE criteria with respect to Testim and can be expected to have the same clinical effect and safety profile when used under the conditions specified in the labeling. Accordingly, Vogelxo is appropriately assigned an A rating. The remaining requests in the Petition are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research