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March 26, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
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CITIZEN PETITION

Auxilium Pharmaceuticals, Inc. ("Auxilium") submits this petition under the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and its implementing regulations to request the Commissioner of Food and Drugs to take the actions described in Section A with respect to therapeutic equivalence rating and labeling of the section 505(b)(2) application filed by Upsher-Smith Laboratories, Inc. ("USL"), No. 204399, for testosterone transdermal gel, 1% ("the proposed product" or "USL's proposed product"), citing Auxilium's product Testim® as the reference listed drug ("RLD"). This citizen petition is based on USL's Patent Certification Notice Letter dated December 21, 2012 and other publicly available information.

A. Actions Requested

Based on USL's claims that its proposed product's penetration enhancers are different from Testim's, Auxilium requests that the Food and Drug Administration ("FDA"):

1. Refrain from designating the proposed product 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 the proposed product has the same safety and effectiveness profiles as Testim;

   b) The proposed product 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 the proposed product is bioequivalent to Testim.

FDA-2013-P-0371

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2. Require that the labeling of USL's proposed product state the proposed product is not interchangeable with other testosterone transdermal gel products.

3. For the reasons set forth in AbbVie's citizen petition in Docket No. FDA-2011-P-0610, refrain from issuing a therapeutic equivalence rating to USL's product 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.[1]

B. Statement of Grounds

I. Summary of Grounds

Auxilium holds an approved new drug application ("NDA") for Testim, a 1% transdermal testosterone gel indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. USL sent to Auxilium a Patent Certification Notice Letter dated December 21, 2012 (the "2012 Patent Notice," attached hereto as Exhibit 2) pursuant to section 505(b)(3) of the FDCA and 21 C.F.R. § 314.52, indicating that USL has filed a 505(b)(2) application referencing Testim. This Patent Notice states that USL's section 505(b)(2) application seeks approval for the same formulation of testosterone gel for which USL previously filed abbreviated new drug application ("ANDA") No. 79-178 – namely a formulation that, according to USL, contains different "penetration enhancers" from Testim. For purposes of this petition, Auxilium assumes that USL's assertions about its proposed formulation are accurate.

In response to Auxilium's earlier citizen petition, dated February 27, 2009, regarding USL's 2008 ANDA, FDA determined that differences in penetration enhancers could cause proposed testosterone gel products to have characteristics different from their RLDs with respect to transfer, hand-washing, showering, and skin irritation and sensitization.[2] FDA noted that the safety implications of differences in transfer potential were not theoretical; indeed, before issuing its response in August 2009, the Agency had received numerous adverse event reports relating to cases of inadvertent testosterone transfer to women and children.[3] Thus, FDA concluded that transfer and hand-washing studies were necessary for all testosterone transdermal gel products to assess whether the proposed products shared the same safety profiles as their RLDs.[4] Similarly, FDA concluded that skin irritation and sensitization studies would be necessary for testosterone gels containing different penetration enhancers than their RLDs.[5]

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[1] *See* Citizen Petition, Abbott Labs. (now AbbVie, Inc.), Docket No. FDA-2011-P-0610 (Aug. 19, 2011) (Exhibit 1).

[2] *See* FDA, Response to Citizen Petition, Docket No. FDA-2009-P-0123 (Aug. 26, 2009), at 4-5, 6, 7.

[3] *Id.* at 4-5.

[4] *Id.*

[5] *Id.* at 7.

Finally, FDA also determined that showering studies would be required in some situations.[6] Because of these requirements, the Agency explained that any application for approval of a testosterone gel product with different penetration enhancers from its RLD must be submitted under section 505(b)(2) of the FDCA rather than as an ANDA.[7]

For similar reasons, FDA should not designate the proposed product as therapeutically equivalent to Testim unless USL makes three showings:

First, USL must submit data showing that its proposed product and Testim have the same safety and effectiveness profiles. This is necessary to justify an "A" rating because therapeutic equivalents must "be expected to have the same clinical effect and safety profile when administered to patients" under the labeled conditions of use.[8] Due to the special safety and effectiveness considerations for testosterone gels, it should not be enough for the proposed product to meet the basic therapeutic equivalence criteria of bioequivalence and pharmaceutical equivalence. As FDA has correctly determined, the proposed product's purported deviations from Testim with respect to alleged "penetration enhancers" may have significant therapeutic implications, particularly with respect to the risk of interpersonal transfer. Therefore, FDA should not assign an "A" rating to the proposed product unless USL submits appropriate data to show that its product has profiles equivalent to Testim in terms of transfer risk, potential to cause skin irritation and sensitization, and the effects of hand-washing and showering on transferability and efficacy.

Second, USL must show that the labeling of its proposed product is the same as the Testim labeling in all material respects. FDA recognizes that the labeling of therapeutic equivalents may differ only in "minor aspects."[9] Discrepancies in labeling content regarding transfer, showering, or skin irritation/sensitization extend beyond the scope of permissible "minor" differences to implicate the safety and effectiveness of the proposed product. Indeed, if the labeling reflects differences in these regards, 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.[10]

Third, USL must submit data showing its product is bioequivalent to Testim.[11] Not only are these data necessary to show that the proposed product meets the basic therapeutic equivalence criteria, they are necessary as a public health matter. Scientific literature shows that testosterone gels that are not bioequivalent may have different clinical effects.

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[6] *Id.* at 6.

[7] *Id.* at 5.

[8] FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* (33rd ed. 2013) ("*Orange Book*"), at vii.

[9] *Id.*

[10] *Id.*

[11] *Id.* at viii.

Fourth, FDA should also require that the labeling of the proposed product state that it is not interchangeable with other transdermal testosterone gel products. Auxilium seeks this change so that the proposed product's labeling would be consistent with labeling currently approved for other testosterone gel products. This disclaimer would highlight for patients and prescribers the existence of important differences among these products, such as transfer potential. The disclaimer is appropriate and necessary, because the USL product will not be interchangeable with the multiple marketed testosterone gel products, even if it is therapeutically equivalent to Testim.

Finally, Auxilium requests that the Agency refrain from issuing an "A" rating to the USL product and to any other drugs described in section 505(b)(2) applications that reference Testim, until the Agency has conducted notice-and-comment rulemaking to establish standards and procedures for issuance and publication of these ratings. Auxilium agrees with AbbVie's citizen petition in Docket No. FDA-2011-P-0610, which describes the grounds for AbbVie's similar request with respect to section 505(b)(2) applications referencing AbbVie's product AndroGel®. Auxilium believes that AbbVie's reasoning is equally applicable to section 505(b)(2) applications referencing Testim.

II. Background

A. Testim Approval

Testim is a prescription transdermal gel containing 1% testosterone as its active ingredient. Testim also contains the following inactive ingredients: purified water, pentadecalactone, carbopol, acrylates, propylene glycol, glycerin, polyethylene glycol, ethanol, and tromethamine. FDA approved Testim in October 2002, pursuant to NDA No. 21-454, for testosterone replacement therapy in adult males with primary hypogonadism and hypogonadotropic hypogonadism. In connection with the Testim NDA, FDA has listed ten patents in the *Orange Book*. The listed patents are owned by FCB I, LLC and licensed to Auxilium.

The Testim labeling includes information about the product's transfer risks, application site reactions, and the effects of showering upon gel efficacy. As explained in the labeling, Auxilium conducted two clinical trials to evaluate the potential for dermal transfer of Testim from treated males to their untreated female partners.[12] In the first trial, males applied Testim to their abdomens and then rubbed abdomen-to-abdomen with their female partners. As the labeling notes, potential for transfer was seen at all time points in this trial.[13] When males used a shirt to cover the abdomen, the potential for transfer was reduced but not prevented. In a second trial where males instead applied Testim to their arms and shoulders, covering the application site with a T-shirt prevented transfer from the male patient to the female partner.[14]

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[12] Testim Prescribing Information, Clinical Pharmacology: Clinical Studies: Potential for Testosterone Transfer (Sept. 2009) (Exhibit 3).

[13] *Id.*

[14] *Id.*

The prescribing information for Testim also contains information on Auxilium's showering study. This study measured the effect of washing with mild soap at 1, 2, and 6 hours after the application of Testim and found that showering reduced testosterone levels.[15] The study did find, however, that serum testosterone levels stayed in the normal range when the showering occurred at least two hours after the patients applied the product.[16] The labeling and Medication Guide for Testim therefore direct the patient to wait at least two hours after application before showering.[17]

Finally, with respect to skin irritation and sensitization, the Testim labeling reports application site reactions observed in the controlled clinical trial of Testim. These reactions occurred in 2% of patients treated with 50 mg Testim, in 4% of patients treated with 100 mg Testim, and in 3% of patients treated with placebo.[18]

B. FDA Action Related to Skin Transfer Risks of Testosterone Gel Products (April 2009)

In May 2009, FDA implemented new requirements for testosterone gels, after the Agency received reports of adverse events stemming from inadvertent testosterone transfer to children.[19] The reported adverse events included the "inappropriate enlargement of the genitalia ... premature development of pubic hair, advanced bone age, increased libido, and aggressive behavior."[20] The Agency stated that some affected children had to undergo "invasive diagnostic procedures," and at least one child was hospitalized and underwent surgery due to difficulties in identifying the root cause of the signs and symptoms. FDA noted that, in most cases, the adverse effects of testosterone exposure regressed after exposure was halted; however, in some cases the effects were irreversible, even once the children were no longer exposed to the product.[21]

Due to the significant public health issues implicated by these adverse event reports, FDA required that transdermal testosterone gel manufacturers add a boxed warning to their drugs' labeling to emphasize the risk of secondary exposure and the steps that should be taken to reduce this risk, including hand washing and covering the application site with clothing.[22] FDA also required manufacturers to develop a Medication Guide as part of a Risk Evaluation and Mitigation Strategy ("REMS").

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[15] *Id.*, Pharmacokinetics: Washing (Sept. 2009).

[16] *Id.*

[17] *Id.*, Dosage and Administration; Testim, Medication Guide (Nov. 2011) (Exhibit 3).

[18] Testim, Prescribing Information, Adverse Reactions, Table 3 (Sept. 2009).

[19] News Release, FDA, *Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide* (May 7, 2009), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm.

[20] *Id.*

[21] *Id.*

[22] *Id.*

C. Original USL Patent Notice Letter, Auxilium Citizen Petition, and FDA Response (February-August 2009)

In connection with the Testim NDA, FDA has listed ten patents in the *Orange Book*. In 2008, USL filed an ANDA citing Testim as the RLD. In connection with that ANDA, USL sent Auxilium a Patent Certification Notice Letter dated October 22, 2008 (the "2008 Patent Notice," attached hereto as Exhibit 4). This Patent Notice explained that USL believed its proposed product would not infringe U.S. Patent No. 7,320,968, based on USL's claim that the proposed product and Testim contained different inactive ingredients characterized by USL as "penetration enhancers."[23]

After receiving the 2008 Patent Notice, Auxilium submitted a citizen petition to FDA asking that the Agency take several actions with respect to USL's ANDA.[24] Among other things, Auxilium requested that FDA require several types of studies—including transfer, hand-washing, showering, and skin irritation/sensitization studies—to confirm that USL's proposed product was not clinically different from Testim despite its claimed different formulation. Auxilium's citizen petition explained that, in light of USL's representations in the 2008 Patent Notice, these studies were necessary to ensure the safety and efficacy of USL's product in comparison with Testim, and to demonstrate that the proposed product could use the Testim labeling. Auxilium also argued that public health considerations supported a requirement of additional testing because of the potential for transfer and the recognized risks of such transfer.

In a response dated August 26, 2009, FDA agreed with Auxilium that variations in penetration enhancers might affect the amount of testosterone gel left on the skin, the rate of absorption in any exposed individual, and the degree of skin irritation and sensitization associated with the gel.[25] In addition, FDA agreed that testosterone transfer to women and children "is a serious concern," due to the "potentially severe and irreversible adverse events" associated with transfer.[26] FDA concluded that "some differences in inactive ingredients" between an RLD and proposed product "including, but not limited to, different penetration enhancers" will "trigger the need for a transfer study to ensure that the proposed product does not have greater transfer potential than the [RLD] as well as a hand-washing study to determine whether hand-washing affects the amount of residual product on the skin."[27] The Agency also announced that it would require showering studies in some instances.[28] Finally, FDA agreed that "skin irritation and sensitization studies are necessary" when a proposed product has different penetration enhancers from its RLD, "to ensure that the proposed product will not cause any more irritation or sensitization than the [RLD]."[29] As a result of these requirements, FDA

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[23] 2008 Patent Notice, at 10.

[24] Citizen Petition, Auxilium Pharms., Inc., Docket No. FDA-2009-P-0123 (Feb. 27, 2009).

[25] FDA, Response to Citizen Petition, Docket No. FDA-2009-P-0123 (Aug. 26, 2009), at 5, 7.

[26] *Id.* at 4, 5.

[27] *Id.*

[28] *Id.* at 6.

[29] *Id.* at 7.

concluded that applicants for these transdermal testosterone gels must submit section 505(b)(2) applications rather than ANDAs to obtain approval.[30]

FDA later reaffirmed these requirements in an October 2010 citizen petition response to Abbott Laboratories, noting that it will continue to require these "human safety studies" to determine whether the transfer risk for a proposed transdermal testosterone gel product is "the same as that of the RLD."[31] FDA also confirmed it would continue to require skin irritation and sensitization studies.[32] The Agency refined its position on showering studies in this citizen petition response, determining that it would require these studies for bioequivalent drugs only when needed to support different labeling.[33]

D. The 2012 Patent Notice

USL sent Auxilium the "2012 Patent Notice," dated December 21, 2012, indicating that it filed a section 505(b)(2) application referencing Testim. The 2012 Patent Notice describes USL's proposed product and provides notice of USL's Paragraph IV certification with respect to ten patents, which USL refers to as "the Gyurik Patents." The 2012 Patent Notice also explains the basis for USL's belief that the Gyurik Patents will not be infringed by the manufacture, use, or sale of the proposed product before their expiration.

1. USL's Contentions Regarding the Proposed Product and Its Differences from Testim

According to the 2012 Patent Notice, "[t]he formulation for which USL seeks approval by NDA 204399 is qualitatively and quantitatively the same formulation that is the subject of USL's ANDA 79-178."[34] Like the 2008 Patent Notice, the 2012 Patent Notice describes USL's proposed product as a transdermal gel containing 1% testosterone as the active ingredient and the following inactive ingredients: ethyl alcohol (anhydrous), glycerin, diisopropyl adipate, methyl laurate, oleyl alcohol, carbomer 980, acrylates, propylene glycol, polyethylene glycol 1000, purified water, and tromethamine.[35]

Like its predecessor, the 2012 Patent Notice also includes a "comparison of the qualitative composition of USL's Testosterone Gel 1% and TESTIM® ...."[36] The 2012 Patent Notice states that both Testim and the proposed product contain testosterone, ethyl alcohol, and several additional components.[37] USL also claims, as it did in 2008, that the proposed product

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[30] *See id.* at 5.

[31] FDA, Response to Citizen Petition, Docket No. FDA-2010-P-0196 (Oct. 4, 2010), at 3.

[32] *Id.* at 4.

[33] *Id.* at 5.

[34] 2012 Patent Notice, at 2.

[35] *Id.* at 1, Appendix 2.

[36] *Id.* at 17.

[37] *Id.* at Appendix 2.

contains three inactive ingredients—diisopropyl adipate, methyl laurate, and oleyl alcohol—that "in contrast are not found in TESTIM®."[38] Similarly, USL again contends that the proposed product "does not contain pentadecalactone (oxacyclohexadecan-2-one), which is included in TESTIM®."[39]

2. USL's Representations Concerning Noninfringement

USL's 2012 Patent Notice indicates that its "basis for non-infringement is the same as was reported to Auxilium ... pertaining to USL's ANDA."[40] Just as in 2008, USL purports to differentiate its proposed product from the claims of the patents on the basis of the type and nature of the alleged "enhancers" identified in each. USL refers to the enhancers in the Gyurik Patents as "Hsieh enhancers," which USL characterizes as "ring-containing molecule[s]."[41] USL asserts that "[n]one of methyl laurate, diisopropyl adipate, and oleyl alcohol contains a ring structure, let alone a macrocyclic ring, and none could be considered a 'Hsieh enhancer.'"[42] USL asserts that "the applicant [for the patent, Gyurik] recognized that his advancement over the art was limited to including . . . a 'Hsieh enhancer,'"[43] and, USL argues, that cannot be construed to cover methyl laurate, diisopropyl adipate, and oleyl alcohol—each of which lacks a ring structure.[44] USL also represents that the proposed product cannot be used to infringe the Gyurik Patents under the doctrine of equivalents because USL's formulation "does not contain 3-methylcyclopentadecanone, 9-cycloheptadecen-1-one, cyclohexadecanone, cyclopentadecanone, oxycyclohexadecan-2-one or colorable equivalents thereof."[45]

III. FDA Should Not Assign an "A" Rating Unless USL Shows that the Proposed Product and Testim Have the Same Safety and Effectiveness Profiles, Have Substantively Identical Labeling, and Are Bioequivalent.

A. Governing Framework: FDA's Therapeutic Equivalence Criteria

The *Orange Book* provides that FDA considers two drugs to be therapeutic equivalents only if: (1) they are pharmaceutical equivalents; and (2) they "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[46] The *Orange Book* also describes four "general criteria" that FDA uses to assign therapeutic equivalence ratings. Namely, FDA generally will rate a

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[38] *Id.* at 17.

[39] *Id.* (emphasis in original).

[40] *Id.* at 2.

[41] *Id.* at 65.

[42] *Id.* at 63.

[43] *Id.* at 65.

[44] *Id.* at 63.

[45] *Id.* at 4.

[46] *Orange Book, at vii.*

product as therapeutically equivalent to its RLD if the drugs are (1) pharmaceutically equivalent;[47] (2) bioequivalent;[48] (3) "adequately labeled"; and (4) manufactured in accordance with current good manufacturing practices (cGMP).

B. Unless USL's Studies Demonstrate That the Proposed Product Has Safety and Effectiveness Profiles Equivalent to Testim, FDA Should Not Designate the Proposed Product as Therapeutically Equivalent to Testim.

Based on the Agency's longstanding definition of therapeutic equivalence, FDA must conclude that USL's proposed product "can be expected to have the same clinical effect and safety profile" as Testim under the labeled conditions of use before granting an "A" rating. Although FDA can often infer that two products meet this standard because they fulfill the Agency's four basic therapeutic equivalence criteria, the Agency has recognized that this approach is sometimes inappropriate. Specifically, FDA has stated that products meeting the basic therapeutic equivalence criteria nonetheless may fail to obtain an "A" rating where the proposed product has "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."[49] For example, oral contraceptives packaged in 21-day packages without placebos and those packaged in 28-day packages with 7 placebos are not therapeutically equivalent, even though they contain the same amount of the same active ingredient, same dosage form, strength, and route of administration.[50]

Taking USL at its word, this is exactly such a case. According to USL's own assertions in its 2012 Patent Notice, the proposed product is alleged to contain different inactive ingredients — including different penetration enhancers — from Testim. FDA has already determined that such differences may have significant therapeutic implications, because they can affect the potential for interpersonal transfer and skin irritation and sensitization and, therefore, the risk of sometimes serious adverse events. Similarly, because of the proposed product's claimed different inactive ingredients, showering after application may cause the proposed product to have different clinical effects. Finally, FDA has already required additional clinical studies (*i.e.*, transfer and hand-washing studies, skin irritation and sensitization studies, and possibly showering studies) to establish the safety and effectiveness of testosterone transdermal gel products. Therefore, USL cannot establish therapeutic equivalence simply by showing that its product meets the four basic therapeutic equivalence criteria listed in the *Orange Book*.

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[47] The *Orange Book* defines "pharmaceutical equivalents" as products that "contain identical amounts of the same active drug ingredient in the same dosage form and route of administration" and "meet compendial or other applicable standards of strength, quality, purity, and identity." *Orange Book*, at vii.

[48] The *Orange Book* defines "bioequivalents" as products that either "do not present a known or potential bioequivalence problem and meet an acceptable *in vitro* standard," or, "if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard." *Id.*

[49] FDA, Response to Citizen Petitions, Docket Nos. FDA-2007-P-0128 & FDA-2009-P-0040 (July 29, 2009), at 4.

[50] *Id.*

Instead, USL must show, through appropriate studies, that its proposed product will have the same safety and effectiveness profiles as Testim, particularly with respect to the potential for interpersonal transfer, skin irritation and sensitization, and the effects of showering. If USL's transfer and hand-washing, or irritation and sensitization, studies show safety or effectiveness differences between the two products, or cannot rule out such differences, then FDA will be unable reasonably to conclude that the proposed product "can be expected to have the same clinical effect and safety profile" as Testim under the labeled conditions of use. Instead, in this case, FDA will have to recognize the potentially significant safety and effectiveness implications of the products' differences. Similarly, if USL's showering study reveals that the serum testosterone levels of a patient using the proposed product vary significantly from those of a patient using Testim under identical washing conditions, then the proposed product and Testim would not have the same effectiveness profiles.

C. FDA Should Not Designate the Proposed Product as Therapeutically Equivalent to Testim if the USL Labeling Differs from the Auxilium Labeling In Any Significant Way.

The labeling of therapeutic equivalents may differ only in "minor aspects," such as "the presence of specific pharmacokinetic information."[51] Because the USL product will require human safety studies and potentially showering studies, its labeling is likely to vary from that of Testim on key issues, not just "minor aspects."

Most importantly, the USL labeling will need to describe the results of the transfer studies. Two recent examples—from the labeling of testosterone gels approved pursuant to section 505(b)(2) applications referencing AndroGel — illustrate the possibility that USL's labeling could differ substantially from Auxilium's with respect to transfer. The AndroGel labeling states that, in clinical studies, transfer was completely prevented when men covered the application site with a T-shirt.[52] In contrast, the labeling of Teva's testosterone transdermal gel product notes that, under these conditions, females showed an 11% increase in testosterone AUC and a 16% increase in testosterone Cmax.[53] Similarly, the labeling for Perrigo's gel indicates that its transfer study showed a 16% increase in testosterone AUC and a 48% increase in testosterone Cmax in the female partners when the application site was covered by a T-shirt.[54] Perrigo's labeling also includes information about skin irritation and sensitization studies that

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[51] *Orange Book*, at vii. *See also* FDA, Response to Citizen Petitions, Docket Nos. FDA-2007-P-0128 & FDA-2009-P-0040 (July 29, 2009), at 3 n.3 (noting that the labeling of pharmaceutical equivalents may differ "within certain narrow limits").

[52] AndroGel 1% for Topical Use Prescribing Information, Pharmacokinetics: Testosterone Transfer from Male Patients to Female Partners (Sept. 2012) (Exhibit 5).

[53] Testosterone Gel, for Topical Use Prescribing Information, Pharmacokinetics: Potential for Testosterone Transfer (Feb. 2012) (Exhibit 6).

[54] Testosterone Gel, for Topical Use Prescribing Information, Pharmacokinetics: Testosterone Transfer from Male to Female Partners (Jan. 2013) (Exhibit 7).

does not appear on AndroGel's labeling.[55] Such labeling differences are critical to the safe use of the product, given the recognized risks of interpersonal transfer, and thus cannot be described as "minor." Differences in labeling regarding skin irritation and sensitization and showering also are not "minor," because they too are important differences relevant to safe and effective use of the products. Indeed, if the labeling reflects differences in any of these regards, 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.[56]

Accordingly, if USL's labeling regarding transfer, application site reactions, or showering after application differs from that of Testim, FDA should not assign an "A" rating to the proposed product. This conclusion accords with FDA's approach to the section 505(b)(2) application for Repronex®. In that case, the applicant had obtained approval of an ANDA for intramuscular (IM) administration, but it conducted additional clinical trials to support a new subcutaneous (SC) route. During labeling negotiations, the sponsor stated its plan to revise the drug labeling, including portions on the IM studies, to reflect these new SC studies. FDA permitted the change but informed the sponsor that it would not permit an A rating for the drug for either the IM or SC use "as a result of [the] new label."[57]

FDA's therapeutic equivalence decision for Clay-Park's mupirocin ointment 2%, now known as Centany®, also is supportive. Centany was intended to be a therapeutic equivalent to the RLD, Bactroban® (mupirocin ointment 2%) for treatment of impetigo.[58] FDA required a section 505(b)(2) application, because clinical studies were needed to address Centany's different vehicle.[59] The products were both topical ointments with the same active ingredient in the same strength for the same indication, and a comparative clinical study showed they were therapeutically equivalent in that indication.[60] The products' labeling differed in an important respect, however. The microbiology subsection of Bactroban's labeling stated that the product had been shown to be "active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus. aureus* (MRSA)."[61] In contrast, Centany's product labeling did not contain the same statement, because Clay-Park declined to provide data supporting

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[55] *Id.* Even if any of these labeling differences is found in the pharmacokinetics section of the labeling, such a difference cannot be classified as minor simply for this reason. Instead, as explained, these labeling differences have important safety and effectiveness implications and would reflect that the products cannot be substituted consistent with patient and prescriber expectations.

[56] *Orange Book*, at vii.

[57] FDA, Group Leader Memorandum Repronex Original NDA, NDA 21-047 (Aug. 12, 1999), at 3.

[58] FDA, Clinical Pharmacology and Biopharmaceutics Review, NDA 50-788 (Nov. 15, 2002), at 1.

[59] *Id.*

[60] FDA, Statistical Review and Evaluation: Clinical Studies, NDA 50-788 (Sept. 18, 2002), at 3.

[61] FDA Response to Citizen Petition, Docket No. 03P-0140 (Nov. 7, 2003), at 7.

effectiveness against MRSA.[62] Despite the sameness in active ingredient and demonstration of therapeutic equivalence for the same indication, FDA assigned a "BX" rating to Centany.[63]

D. If USL's Proposed Product Fails to Establish Its Bioequivalence to Testim, It Should Not Be Rated as Therapeutically Equivalent.

If the USL product is not bioequivalent to Testim, FDA cannot rate it as therapeutically equivalent. Not only would such a rating be inconsistent with FDA's basic therapeutic equivalence criteria, but it would also be unsafe.

As literature on Testim and AndroGel demonstrates, transdermal testosterone gel products that are not bioequivalent may have significantly different clinical effects. Grober et al., assessed the medical records of 370 men who switched between AndroGel and Testim, which are not bioequivalent.[64] In the study, patients who switched from AndroGel to Testim experienced a significant increase in total and free serum testosterone levels, but patients switching from Testim to AndroGel did not. The authors concluded that replacing AndroGel with Testim would give hypogonadal men "the potential for improved clinical and biochemical responsiveness," whereas substituting AndroGel for Testim could be "attempt[ed] to eliminate or minimize unwanted side effects but is less likely to offer patients significant symptomatic or biochemical improvements."[65] The authors attributed these differences to the products' distinct pharmacokinetic differences stemming from "the enhanced absorption of Testim ... attributed to pentadecalactone."[66] Thus, a lack of bioequivalence can cause clinical differences between products with the same active ingredient. For this reason, FDA cannot and should not rate the proposed product as therapeutically equivalent to Testim unless USL shows bioequivalence.

IV. FDA Should Require That USL's Labeling State That the Proposed Product Is Not Interchangeable With Other Testosterone Transdermal Gel Products.

Numerous testosterone gel products bear similar labeling regarding their non-interchangeability. The AndroGel labeling contains the following two statements: (1) "The application site and dose of AndroGel 1% are not interchangeable with other topical testosterone products," and (2) "Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure."[67] The Fortesta® labeling

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[62] *Id.*

[63] *Orange Book*, at 3-300.

[64] E.D. Grober et al., Efficacy of Changing Testosterone Gel Preparations (Androgel or Testim) Among Suboptimally Responsive Hypogonadal Men, 20 INT. J. IMPOT. RES. 213, 216 (2008) (Exhibit 8).

[65] *Id.* at 213, 216-17.

[66] *Id.* at 216.

[67] AndroGel 1% for Topical Use Prescribing Information, Indications and Usage & Dosage and Administration: Dosing and Dose Adjustment (Sept. 2012).

states that "FORTESTA is not interchangeable with other topical testosterone products,"[68] and the Axiron® labeling contains the same message about interchangeability.[69] In connection with a pending labeling supplement, FDA and Auxilium are discussing the addition of similar conforming statements to the Testim labeling.

FDA should require similar labeling statements for USL's product. In particular, the labeling for USL's product should state that it is not interchangeable with other testosterone gels. The USL product, like Testim, is likely to have substantial differences from these other gels, even if it is therapeutically equivalent to Testim. For example, the USL product could differ from other marketed testosterone gels in transfer and hand washing, irritation and sensitization, and efficacy after showering. Indeed, due to such differences, FDA has proposed to add to the Testim labeling similar content on non-interchangeability to that found in the labeling of several other testosterone gels. Given that the USL product relies upon the Testim approval, it would therefore be appropriate to include this content in the USL labeling, whether or not the USL product is therapeutically equivalent to Testim. Moreover, the proposed product may differ from Testim in some or all of these respects, further heightening the need for such labeling.

Including these common non-interchangeability statements in the proposed product's labeling will help ensure that prescribers and patients are aware of the differences. Switching among products could expose patients to different risks and benefits, and prescribers and patients should be informed of this possibility. Omitting these non-interchangeability statements from the proposed product's labeling would instead confuse patients, undercut the effectiveness of the non-interchangeability content in the above labeling, and create the possibility of improper substitutions. FDA's overarching concerns with interchangeability within the class of testosterone gels, as reflected in this labeling, provide further support for the conclusion that the USL product should not receive an "A" rating. If FDA issued this rating, doctors, pharmacists and patients would need to distinguish between interchange of Testim and the USL product versus interchange of Testim and other testosterone gel products. This situation would potentially lead to confusion and inappropriate substitutions.

V. FDA Must Conduct Notice-and-Comment Rulemaking Before Issuing "A" Ratings for 505(b)(2) Applications Referencing Testim.

Auxilium agrees with AbbVie's citizen petition in Docket No. FDA-2011-P-0610 and believes that the reasoning of this petition is equally applicable to drugs described in 505(b)(2) applications referencing Testim.

AbbVie argues that FDA must conduct notice-and-comment rulemaking before issuing therapeutic equivalence ratings to drugs described in section 505(b)(2) applications that

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[68] Fortesta Gel for Topical Use, Prescribing Information, Highlights, Dosage and Administration (Dec. 2012) (Exhibit 9).

[69] *See* Axiron Topical Solution, for Topical Use Prescribing Information, Dosage and Administration: Dosing and Dosing Adjustment (Dec. 2011) (Exhibit 10) ("The application site and dose of AXIRON are not interchangeable with other topical testosterone products.").

reference AndroGel.[70] According to AbbVie, this rulemaking should establish standards and procedures for issuance and publication of these ratings.[71] As AbbVie notes, more than three decades ago, FDA concluded that therapeutic equivalence ratings are merely "nonregulatory evaluations that are based on the application of certain criteria to information contained in FDA files" and thus, do not require notice-and-comment rulemaking.[72] Auxilium agrees with AbbVie that therapeutic equivalence ratings are no longer "non-regulatory," if they ever were, because they are incorporated into state substitution laws and directly affect reimbursement levels under federal health care programs. We also agree that, for 505(b)(2) drugs, these ratings are not based on information already in FDA's files. Although FDA arguably must determine whether an ANDA meets the four therapeutic equivalence criteria to determine whether it is approvable, this is not the case for section 505(b)(2) applications. Instead, FDA need only determine whether these products are safe and effective.

Auxilium thus agrees with AbbVie's petition and believes AbbVie's conclusions are appropriately applied to section 505(b)(2) applications referencing Testim. We therefore request that, before granting therapeutic equivalence ratings to drugs described in section 505(b)(2) applications, the Agency conduct notice-and-comment rulemaking to establish standards and procedures for these ratings.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only at the request of the Commissioner.

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[70] *See* Citizen Petition, Abbott Labs. (now AbbVie, Inc.), Docket No. FDA-2011-P-0610 (Aug. 19, 2011), at 2.

[71] *Id.*

[72] *Id.* at 11 (citing 45 Fed. Reg. 72582, 72587 (Oct. 31, 1980)).

E. Certification[73]

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Pursuant to 21 U.S.C. § 355(q)(1)(H), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: December 24, 2012, when Auxilium first received notice of USL's pending section 505(b)(2) application for a testosterone transdermal gel product that relies on Testim as the reference listed drug. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on behalf of Auxilium as part of my responsibilities as an employee of Auxilium; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

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[73] Auxilium believes that this petition is not subject to section 505(q) of the FDCA, because Auxilium is not asking that FDA take any action that could delay approval of the proposed product. *See* FDCA § 505(q)(1)(A); FDA, *Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 7 (June 2011) (noting that FDA "interpret[s] section 505(q) to apply only to petitions that request an action that could delay approval of a pending ANDA or 505(b)(2) application"). Instead, Auxilium asks only that FDA refrain from designating the proposed product as therapeutically equivalent to Testim if and when the Agency approves USL's proposed product. Nonetheless, out of an abundance of caution and in order to avoid delay if FDA concludes that section 505(q) is applicable, Auxilium has provided the certification required by section 505(q)(1)(H) of the FDCA.